THE IDENTIFICATION OF HAEMORRHAGIC AND ISCHAEMIC STROKE BY NEUROIMAGING: PRESENT PRACTICE AND FUTURE NEEDS

Sarah Louise Keir

Doctor of Medicine
University of Edinburgh
2002

For my father, Jack Keir

Abstract

Neuroimaging with computed tomography (CT) and magnetic resonance imaging (MRI) has markedly improved the accuracy of diagnosis of stroke and its underlying causes. As more treatment options and advanced imaging modalities, such as diffusion-weighted MRI (DWI) and magnetic resonance perfusion imaging (PI) become available, it becomes increasingly important to have an accurate idea of the capability of each modality in order that the best use is made of a limited resource. Using a combination of systematic review and new data, this thesis clarifies the strengths and limitations of CT, conventional MRI and DWI in the diagnosis of intracerebral haemorrhage (ICH) and ischaemic stroke.

The thesis is divided into three sections. The first section explores the consequences of not using conventional neuroimaging (CT or MRI) in stroke, both for research and patient care. Chapter 2 investigates the potential effect of different scanning policies on stroke incidence studies and finds that because of too little neuroimaging, or the use of CT at a later time than when it could reliably detect haemorrhage, epidemiological studies could be flawed in the estimation of the frequency of ICH. Chapter 3 explores the effect on patient outcome of not identifying haemorrhage and commencing antithrombotic therapy for secondary prevention as for ischaemic stroke, and finds that although aspirin may be beneficial and heparin is likely not to be, the data are lacking to be certain.

The second section explores the sensitivity of CT and conventional MRI in the identification of haemorrhage. Systematic reviews of CT and conventional MRI reveal the lack of robust data and weak study methods in imaging studies, making it impossible to make a quantitative judgement of sensitivity. Two new studies, including the largest study to date to directly compare CT and conventional MRI, demonstrate that signs of haemorrhage that disappear from CT remain visible on certain MR sequences, most notably gradient-echo imaging, for years if not indefinitely. Also, in patients with minor stroke scanned an average of three weeks after symptoms, CT missed ICH in 75% of cases identified on MRI, and this had consequences for clinical decision-making.

The third section explores the capabilities of CT, conventional MRI and DWI to positively identify ischaemic stroke. A systematic review of published studies of sensitivity of CT and conventional MRI in the positive identification of ischaemic stroke reveal widely varying values for sensitivity for both CT and MRI with little direct comparisons. Data from our own study comparing CT and MRI in minor strokes demonstrates a similar efficacy for each modality. A systematic review of the literature on DWI and PI in the positive identification of ischaemic stroke reveal that though highly promising, the data are not available to determine their clinical advantage over conventional imaging. A new study of patients undergoing DWI following stroke demonstrates the clinical utility of DWI over and above standard scanning techniques, and the effect of clinical severity of stroke on the sensitivity of DWI.

PREFACE 5

1 BACKGROUND 10

1.1 Introduction 10

1.2 The Anatomy And Pathology Of Stroke 10

1.2.1 Cerebral vascular anatomy 10

1.2.2 Pathology of stroke 12

1.3 The Pathophysiology Of Stroke 13

1.3.1 Normal cerebral metabolism 13

1.3.2 Cerebral metabolism in the ischaemic brain 15

1.3.3 Intracerebral haemorrhage 18

1.4 The Clinical Examination And Its Limitations 19

1.5 Principles Of Computerized Tomography And Magnetic Resonance Imaging 21

1.5.1 Computerised tomography (CT) 21

1.5.2 Magnetic resonance imaging (MRI) 22

1.6 Pathological Changes Seen On Neuroimaging 24

1.6.1 Ischaemic stroke 24

1.6.2 Intracerebral haemorrhage 26

1.6.3 Haemorrhagic transformation 29

1.7 Summary 30

2 THE IMPORTANCE OF NEUROIMAGING IN MAKING AN ACCURATE DIAGNOSIS IN PATIENTS WITH STROKE SYMPTOMS 35

2.1 Introduction 35

2.2 Methods 38

2.2.1 The proportion of stroke mimics in populations of patients presenting with stroke 38
2.2.2 Scanning policies in stroke incidence studies 39

2.3 Results 40
2.3.1 The proportion of stroke mimics in populations of patients presenting with stroke 40
2.3.2 Scanning policies in stroke incidence studies 41

2.4 Discussion 44

3 THE IMPORTANCE OF DIAGNOSIS OF INTRACRANIAL HAEMORRHAGE IN PATIENTS BEING CONSIDERED FOR ANTITHROMBOTIC TREATMENT 55

3.1 Introduction 55

3.2 Methods 56

3.3 Results 58

3.4 Discussion 67

4 THE SENSITIVITY OF CT AND MRI IN THE IDENTIFICATION OF INTRACEREBRAL HAEMORRHAGE 74

4.1 Introduction 74

4.2 Methods 75

4.3 Results 77
4.3.1 CT and the identification of haemorrhage 77
4.3.2 MRI and the identification of haemorrhage 80
4.3.3 Studies that directly compared CT and MRI 80

4.4 Discussion 82

5 CHANGES OVER TIME IN CT AND MRI IN THE DETECTION OF INTRACEREBRAL HAEMORRHAGE 96

5.1 Introduction 96

5.2 The Late Haemorrhage Study 98
5.2.1 Methods 98
5.2.2 Results 100

5.3 The CT Versus MRI Study 103
5.3.1 Methods 103
5.3.2 Results 106

5.4 Discussion 119

6 THE SENSITIVITY OF CT AND CONVENTIONAL MRI TECHNIQUES IN MAKING A POSITIVE DIAGNOSIS OF ISCHAEMIC STROKE 135

6.1 Introduction 135

6.2 Methods 136

6.3 Results 137
6.3.1 Studies of CT alone in the identification of ischaemia 137
6.3.2 Studies of conventional MRI alone in the identification of ischaemia 140
6.3.3 Studies of both CT and MRI in the identification of ischaemia – existing data 140
6.3.4 The CT versus MRI study – new data on the positive identification of ischaemia 142

6.4 Discussion 143

7 THE SENSITIVITY OF DIFFUSION-WEIGHTED IMAGING AND PERFUSION IMAGING IN THE IDENTIFICATION OF ISCHAEMIC STROKE. 165

7.1 Introduction 165

7.2 Methods 168

7.3 Results 169

7.3.1 Studies of diffusion-weighted imaging alone 169

7.3.2 Studies of perfusion imaging alone 172

7.3.3 Studies of DWI and PI in combination 173

7.3.4 Data from more recently published studies 174

7.4 Discussion 175

8 DIFFUSION-WEIGHTED MAGNETIC RESONANCE IMAGING IN STROKE - EXPLORATORY ANALYSES FROM OUR OBSERVATIONAL CASE SERIES 194

8.1 Introduction 194

8.2 Methods 195

8.3 Results 200

8.3.1 The utility of DWI 200

8.3.2 DWI and stroke severity 204

8.4 Discussion 210

SUMMARY 220

ACKNOWLEDGEMENTS 223

MY CONTRIBUTION TO THIS THESIS 224

APPENDICES AND PUBLICATIONS 225

Preface

Over the last decade, there has been a major shift in the approach to stroke care, as services have become more organised and guidelines established on best practice[1,2]. However, there is still considerable variation in certain aspects of stroke management, particularly in the use of neuroimaging. At the moment, brain scanning with either computed tomography (CT) or magnetic resonance imaging (MRI) is used in patients with stroke chiefly to exclude important non-stroke pathology that may mimic stroke symptoms (e.g. cerebral tumour), and to identify intracranial haemorrhage, thereby avoiding inappropriate treatment. With the advent of thrombolysis for the treatment of acute ischaemic stroke, there is an increasing need for better methods to make a positive diagnosis of ischaemic stroke quickly and reliably[3]. This may mean that in the near future, a 'negative' scan combined with the clinical signs of a stroke may not be enough to plan further patient management appropriately. Advanced imaging modalities such as magnetic resonance diffusion-weighted imaging (DWI) and perfusion imaging (PI) are thought[4] to be superior to conventional imaging in the positive identification of ischaemic stroke and may thus represent the next stage in the evolution of neuroimaging in stroke.

At present, the majority of patients with stroke in the United Kingdom who undergo diagnostic imaging will have a CT scan. Only occasionally will conventional MRI be used. More advanced imaging modalities are currently limited to only a few major teaching hospitals. However, the use of CT in stroke has dramatically increased over the last ten years, and the use of MRI is also increasing[5,6]. Precisely how we should be scanning in stroke (e.g. timing and type of scan) is still under debate. Imaging is a relatively expensive and limited resource that has to attempt to meet numerous competing demands from different specialities. Stroke is a common medical problem. To make best use of limited resources it is essential to understand the capabilities of the different imaging modalities in stroke.

The aim of this thesis is to evaluate the strengths and limitations of CT, conventional MRI, and DWI in the diagnosis and management of stroke, thereby enabling the Stroke Physician to make a more informed judgement about choice of imaging, or to have a

better idea of what information an available imaging modality can deliver. It does not aim to explore the cost or organisational implications of differing scanning policies. Study methods will focus on addressing three key questions:

1. What would be the effects of not using scanning?

Without neuroimaging, the diagnosis of stroke and its underlying cause will be inaccurate in a proportion of cases. Several studies demonstrating the improved distinction of stroke from non-stroke (stroke 'mimics'), and intracerebral haemorrhage (ICH) from ischaemic stroke, by clinicians when scanning is available are reviewed in chapter 2. Further information on the proportion of stroke mimics in stroke populations, and the relative importance of stroke expertise in the diagnosis of stroke gained from systematic reviews of the literature will be presented.

A number of systematic reviews were performed during the course of this research. This method, pioneered in the investigation of randomised controlled trials[7], aims to determine as comprehensively as possible the data available on a given subject and thereby minimise the potential bias of a more selective review. The principles of performing a systematic review are: to define the question to be addressed; to use a defined search strategy to identify relevant studies; to select studies and extract data using explicit criteria, and if possible, to synthesise evidence in a quantitative manner[8].

Systematic review is less often used in the analysis of imaging literature. However, although radiological studies are by their nature mainly observational, robust methodology can still be applied, and by doing so, will produce better quality data. For example, during imaging patients may move (decreasing the quality of the image), or be unable to tolerate the scanner, and certainly there will be patients in whom MRI is contraindicated. A retrospective collection of high quality scans does not give a realistic impression of the sensitivity or practicality of a mode of scanning in a non-selected stroke population. Also, although having knowledge of clinical history when interpreting an image is clinically realistic, using other imaging against which to compare scans would falsely increase the accuracy of results. Systematic review can be used to assess the quality of available evidence and identify where more research or better methodology is needed. A good stroke imaging study should give clear details of: its

aim; the definition and characterisation of its study population (e.g. severity and type of ischaemic stroke); the technical details of the imaging tests; whether the analysis was prospective or retrospective; the timing of scanning in relation to onset of stroke symptoms; how the images were analysed and read, and by whom; whether the reading was blinded to clinical details and other imaging, and if comparisons within the study population are made, an objective statistical analysis should be used to compare the populations with a null hypothesis being clearly stated. Throughout this thesis, imaging studies will be examined for their attention to objective study methods.

The inadequacy of clinical judgement alone in distinguishing ICH from ischaemic stroke has important consequences both for research and patient care. In the remainder of chapter 2, the potential effect of different scanning policies on stroke incidence studies is explored; the hypothesis being that because of an inadequate approach to the use of neuroimaging, studies of the frequency of stroke may have underestimated the incidence of ICH. This will be tested by performing a systematic review of the scanning policies in prospective community-based stroke incidence studies and will incorporate revised estimates of the incidence of ICH.

Chapter 3 explores the effect on patient outcome of not identifying haemorrhage and commencing antithrombotic therapy for secondary prevention as for ischaemic stroke. The hypothesis is that the effect of antithrombotic agents (antiplatelet drugs or anticoagulants) is qualitatively different in patients with ICH compared to that of patients with ischaemic stroke. A systematic review of all randomised controlled trials of antithrombotic agents in patients with intracranial haemorrhage, combined with unpublished data from the International Stroke Trial[9] and Chinese Acute Stroke Trial[10] will collate all available evidence of the effects of antithrombotic drugs on intracranial haemorrhage.

2. What are the relative sensitivities of CT and MRI in the detection of ICH?

The hypothesis is that the optimum imaging modality for the diagnosis of ICH will vary between CT and MRI depending upon the timing of scanning after onset of stroke symptoms and the clinical status of the patient. This will be tested using three different strategies:

- A systematic review of the existing literature of the sensitivity of CT and MRI in the identification of ICH will be performed (chapter 4). All data on feasibility and tolerability of scanning will also be extracted.
- A prospective observational study of the sensitivity of MRI to detect evidence of haemorrhage in patients with known ICH months after their index event (chapter 5).
- A prospective observational study comparing the capability of CT and MRI to make a positive diagnosis of ICH in 228 patients presenting with minor stroke (chapter 5).

3. What are the relative sensitivities of CT and MRI in the positive identification of ischaemic stroke?

The hypothesis is that MRI, whether it be conventional imaging or DWI, is more sensitive than CT in the positive identification of ischaemic stroke. This will be tested using four strategies:

- A systematic review of published studies of sensitivity of CT and conventional MRI in the positive identification of ischaemic stroke. This will also incorporate information on the inter-observer reliability of scan interpretation (chapter 6).
- Data from our own study of CT versus MRI in minor strokes, on the relative capabilities of each to make a positive diagnosis of ischaemic stroke (chapter 6).
- A systematic review of the literature on DWI and PI in the positive identification of ischaemic stroke (chapter 7).
- A prospective observational case series of patients undergoing DWI following stroke that will focus on two issues: the clinical utility of DWI over and above standard scanning techniques, and the effect of clinical severity of stroke on the sensitivity of DWI (chapter 8).

In summary, neuroimaging has markedly improved the accuracy of diagnosis of stroke and its underlying causes. As more treatment options and imaging modalities become available, it becomes increasingly important to have an accurate idea of the capability of each modality in order that the best use is made of a limited resource. Using a combination of systematic review and new data, my thesis aims to clarify the strengths and limitations of CT, conventional MRI and DWI in order to do so.

1. Royal College of Physicians. Recommendations for acute treatment of stroke. BMJ 2000;320:823-5.

2. Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with stroke. I: Assessment, investigation, immediate management and secondary prevention. SIGN publication number 13. 1997. Edinburgh, SIGN.

3. Wardlaw, J. M., Yamaguchi, T., and del Zoppo, G. J. Thrombolytic therapy versus control in acute ischaemic stroke (Cochrane Review). The Cochrane Library (3). 1998. Oxford, Update software.

4. Hacke W,.Warach S. Diffusion-weighted MRI as an evolving standard of care in acute stroke. Neurology 2000;54:1548-9.

5. Ebrahim, S. and Redfern, J. Stroke Care - a matter of chance. A national survey of stroke services. 1999. London, The Stroke Association.

6. Lindley R, Amayo E, Marshall J, Sandercock PAG, Dennis M, Warlow CP. Hospital services for patients with acute stroke in the United Kingdom: the Stroke Association Survey of Consultant opinion. Age & Ageing 1995;24:525-32.

7. Peto R, Collins R, Gray R. Large-scale randomized evidence: large, simple trials and overviews of trials. J.Clin.Epidemiol. 1995;48:23-40.

8. Warlow CP, Dennis MS, van Gijn J, Hankey GJ, Sandercock PAG, Bamford JM et al. Specific treatment of acute ischaemic stroke. Stroke. A practical guide to management , p 465. Oxford: Blackwell Science Ltd, 2001.

9. Anonymous. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet 1997;349:1569-81.

10. Anonymous. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet 1997;349:1641-9.

1 Background

1.1 Introduction

The World Health Organization definition of stroke is 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin[1]. It is not a new disease; Hippocrates used the term 'apoplexy' to describe the sudden cataclysmic event and subsequent paralysis that we would recognise as a stroke today[2]. The annual incidence of stroke varies worldwide between approximately 300/100 000 to 500/100 000 for subjects aged between 45 and 84, the rate increasing with age[3]. It is the third commonest cause of death (after coronary heart disease and cancer)[4], and the leading cause of severe disability in the community[5]. Based on epidemiological studies, between 73 and 86% of strokes are due to ischaemic stroke, between 8 to 15% to primary intracerebral haemorrhage (PICH), and one to five percent to subarachnoid haemorrhage[3]. This chapter will explore the pathophysiological processes that culminate in stroke symptoms, the capabilities and limitations of clinical judgement alone in the distinction of stroke from other conditions that can present with similar symptoms as well as stroke subtype, and the reasons why neuroimaging can be of value in achieving the correct diagnosis.

1.2 The Anatomy And Pathology Of Stroke

1.2.1 Cerebral vascular anatomy

The brain receives its blood supply from two pairs of vessels: the internal carotid arteries, and the vertebral arteries. The internal carotid arteries arise from the common carotid arteries, which on the right arises from the brachiocephalic trunk, and on the left directly from the aortic arch. The vertebral arteries arise from the subclavian arteries (figure 1) and, after passing through the foramen magnum of the skull, fuse into a single midline vessel, the basilar artery. From the vertebrobasilar system, arises the anterior spinal artery, the paired anterior and posterior inferior cerebellar arteries, superior cerebellar arteries, and arteries to the brainstem. The basilar artery finally divides into

the two posterior cerebral arteries. The internal carotid and vertebral arteries, are linked at the skull base by an interconnecting set of vessels to form the circle of Willis (figure 2). These four principal arteries give rise to the right and left anterior, middle and posterior cerebral arteries.

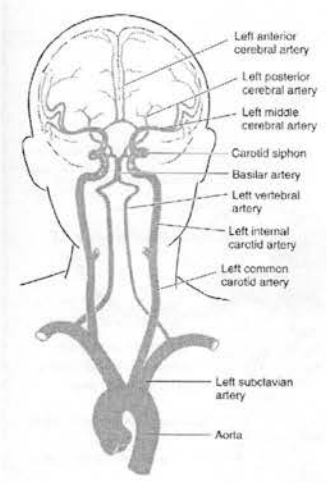


Figure 1. Major cerebral arteries . S.G.: Correlative neuroanatomy, Lange[6])

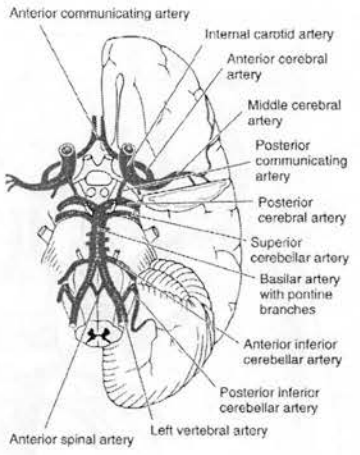


Figure 2: circle of Willis (reproduced from Waxman,

The internal carotid artery enters the skull via the carotid canal, curving forward through the cavernous sinus, then up through the dura into the brain. The first vessel given off is the ophthalmic artery, followed by the posterior communicating artery and the anterior choroidal artery, both also arising directly from the internal carotid. It then divides into its two terminal branches, the anterior and middle cerebral arteries.

The *anterior cerebral arteries* course around the genu of the corpus callosum, supplying the anterior frontal lobes and medial aspect of the cerebral hemispheres. They are connected by the anterior communicating artery, which becomes an important route of collateral supply in the event of occlusion of an internal carotid. The *middle cerebral artery* supplies around 70% of the hemisphere cortex, and is divided neuroradiologically into several regions: the first part (the M1 segment) runs horizontally following the Sylvian fissure and gives off multiple small terminal penetrating arteries with virtually no collateral circulation (lenticulo-striate arteries), the second segment (M2) runs through the insular cortex, and then as it branches further, segments are termed M3 to M5[7]. The *posterior cerebral artery* curves around the brainstem, supplying the occipital lobe and the

choroid plexus of the third and fourth ventricles, the lower surface of the temporal lobe and the midbrain (figure 3).

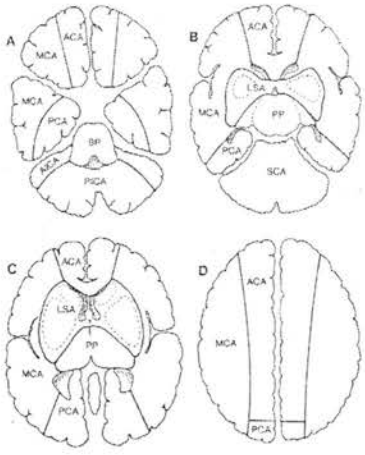


Figure 3. Left: Diagram of vascular territories as depicted in four axial sections. ACA: anterior cerebral artery, MCA: middle cerebral artery, PCA: posterior cerebral artery, LSA: lenticulostriate arteries, PP: posterior perforators, SCA: superior cerebellar artery, PICA: posterior inferior cerebellar artery, BP: basilar perforators (adapted from Cinnamon 1995[8])

The descriptions above are simplified descriptions of the anatomy of the cerebral vasculature. Autopsy studies have demonstrated that in reality, there is great variability in the size and supply zone of various arteries. Anomalies of the circle of Willis are frequent; the most common anomaly of the posterior communicating artery for instance, is its direct origin from the internal carotid artery occurring in around 20 percent of people[9]. The territories supplied by each vessel also vary[10], therefore when a lesion is found on neuroimaging, it may not always be possible to infer which vessel is affected from the site of the lesion or whether the lesion is in the borderzone of two territories.

1.2.2 Pathology of stroke

Causes of stroke

Ischaemic stroke (or cerebral infarction) is the result of acutely reduced cerebral perfusion, which can be provoked either by occlusion of a cerebral artery (ischaemic stroke) or a fall in cerebral blood flow by other means. The most common causes of occlusion of a cerebral artery are local thrombus formation or thromboembolus from a distant site. Thrombus formation is thought to be triggered by vascular endothelial damage, either due to erosion of endothelium or rupture of an atherosclerotic plaque. The exposure of subendothelial structures then activates platelet adhesion and blood

coagulation factors leading to acute thrombus[11]. Areas prone to the build-up of clot or atheroma are important sources of thromboembolus as friable tissue can break free, enter the cerebral circulation and block cerebral arteries. Common sites for atherosclerotic or clot build-up include the origin of the internal carotid arteries, the arch of the aorta, and the heart.

The other common type of stroke, intracerebral haemorrhage (ICH) is caused by the extravasation of blood through a critically weakened area of an intracerebral blood vessel. There are many factors that may contribute to a reduction in the integrity of the vessel wall such as the degenerative vascular changes seen in hypertension[12] and amyloid angiopathy[13]. Other factors may then predispose the vessel to rupture (for example acute hypertension or sympathomimetic drugs), or exacerbate haemorrhage once it has occurred (anticoagulation)[14].

1.3 The Pathophysiology Of Stroke

1.3.1 Normal cerebral metabolism

Energy production

To function, biological systems need energy in the form of adenosine triphosphate (ATP) and the richest source of it is the aerobic metabolism of glucose. The brain, unlike other organs, uses only glucose as a substrate for energy production. In the presence of oxygen, glucose is metabolised by a series of reactions to pyruvate. During this process, the oxidised form of nicotinamide-adenine dinucleotide (NAD^+) is reduced (NADH). Pyruvate is then oxidised in the mitochondria to carbon dioxide (CO_2) and water (H_2O) with the resulting formation of 36 moles of adenosine triphosphate (ATP) for every mole of glucose metabolised. If there are inadequate levels of oxygen (hypoxia), this does not occur and instead, pyruvate is converted to lactate with the production of far less ATP (two moles for each mole of glucose)[15].

Cerebral energy demand

The brain has a high metabolic rate, using about 125g of glucose per day and not surprisingly has an extremely rich blood supply, utilising 15-20% of the total cardiac output[16]. This is an entirely disproportionate amount in relation to the relative weight of the brain in comparison to the total body weight (about 2%). Global cerebral blood flow (CBF) is about 50ml/100mg/minute, with relatively higher values in the young (less than 20 years) and lower values in the older (greater than 60 years). Grey matter has a higher CBF compared to white matter due to its higher metabolic rate[17]. The amount of oxygen extracted from the blood (oxygen extraction fraction, OEF) can vary in times of increased metabolic demand, but under normal circumstances remains roughly constant at around one third[18].

Cerebral autoregulation

In the normal brain, CBF is maintained at a constant level, regardless of variations in systemic arterial pressure in order to ensure a constant energy and oxygen supply. In the normal brain, CBF is kept constant by the dynamic relationship between cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR), as described by the formula:

$$CBF = \frac{CPP}{CVR}$$

The CPP is the difference between arterial pressure, forcing blood into the cerebral circulation, and venous backpressure. CPP can be reduced by dropping arterial pressure, or increasing intracranial pressure (ICP). Normally venous backpressure is negligible and CPP equals arterial blood pressure. Usually changes in CPP over a wide range have little effect on CBF due to alteration of CVR, a system termed 'autoregulation'. As cerebral vessels dilate, CBF (and cerebral blood volume, CBV) increase, and decrease when vessels constrict. The normal range of mean arterial blood pressure over which this system works is around 60 to 150 mmHg. If the capacity for cerebral vessels to autoregulate is lost, the CBF through these vessels becomes directly dependent upon systemic arterial pressure. In this situation, a small reduction in systemic arterial pressure can lead to a marked reduction in cerebral perfusion[19].

1.3.2 Cerebral metabolism in the ischaemic brain

Ischaemia at a molecular level

In the hypoxic brain, anaerobic production of ATP leads to the accumulation of lactate and unbuffered hydrogen ions, altering the acid-base status of the tissue. As energy demands outstrip the capacity to make ATP, energy-dependent mechanisms including ion pumps fail, leading to the deterioration of membrane ion gradients and equilibration of intracellular and extracellular ions (anoxic depolarisation). As a consequence, potassium ions move out of the cell, sodium and calcium move into the cell, and excitatory neurotransmitters such as glutamate and aspartate are released in potentially neurotoxic concentrations[20]. These metabolic disturbances lead to a rise in cell osmolality, causing shifts of water into the intracellular compartment[21].

Changes in cerebral blood flow in ischaemia – luxury versus misery perfusion

In ischaemic stroke, when cerebral blood flow is suddenly reduced, changes occur in cerebral perfusion (CBF), and tissue oxygen consumption ($CMRO_2$). Animal studies have identified four patterns of compensation[22]:

1. Cerebral blood volume is increased to maintain CBF (autoregulation). The brain's dense network of collateral vessels may contribute to this, even producing areas of relatively or absolutely increased CBF, termed 'luxury perfusion'.
2. Reduced CBF with a relatively preserved $CMRO_2$, achieved by increasing the oxygen extraction fraction (OEF), a situation known as 'misery perfusion'.
3. Reduced CBF *and* $CMRO_2$ in spite of increased OEF, which results in the development of ischaemia.
4. Very low levels of CBF and $CMRO_2$ leading to cell death[22].

Degree of ischaemia is important; introducing the ischaemic penumbra

The degree of ischaemia that the brain could tolerate began to be explored on a scientific basis in the 1970s, when it was noted that in patients undergoing carotid endarterectomy, the EEG of the patient flattened when CBF was reduced to around a third of normal[23]. Animal models showed that although the brain demonstrated loss of electrical function at a CBF of around 20ml/min/100g, it was not until lower rates of

CBF of around 10ml/min/100g that there was failure of sodium/potassium ion pumps with potassium release indicating membrane failure and cell death[24]. The functionally silent but still viable tissue in between these two limits was named the 'ischaemic penumbra' and raised hopes that therapeutic interventions could be developed to salvage it before cell death occurred. As this situation was studied further, it became clear that cell metabolism is affected before it becomes clinically evident, with different brain and cellular functions breaking down at varying CBF levels[25].

Duration of ischaemia is important; the ischaemic penumbra is a dynamic concept

Following on from the discovery that the degree of reduction in CBF was important in determining the extent of tissue damage, studies in monkeys demonstrated that these CBF thresholds were not rigidly fixed, and that they also depended upon the length of time for which the CBF remained at a certain level[26]. In one study for instance, tissue with a CBF of 15ml/100mg/min could withstand about three hours of reduced blood flow before infarcting, whereas in tissue with a CBF of 5ml/100g/min infarction occurred after only two hours[27]. This introduced the concept of a region of ischaemia as an ongoing dynamic process, far more complex than originally thought.

The size and shape of the ischaemic penumbra are controversial; various studies have come to differing conclusions. One group noted volumes representing up to 65% of the affected tissue to be within the 'penumbral range' (as determined by reduced CBF and increased OEF) and to be demonstrable for up to 16 hours following the initial insult[28]. Others (defining penumbra as tissue with an OEF of 50 to 70%) found much smaller volumes that could be considered penumbra and raised doubts as to its importance[29]. It is also not clear whether all salvageable tissue is situated in a 'rim' around an infarcted core, or whether the zone at risk is comprised of islands of ischaemic and infarcted tissue. The differing criteria used to define the penumbra will almost certainly contribute to the variance in these results. This remains a source of intense debate, with considerable doubt being expressed as to the merit of using the OEF in the definition of the penumbra[30]. This issue must be resolved; if different criteria are used to define the penumbra, it follows that different environments will be studied, which will make interpretation of findings on neuroimaging impossible. Once

an accurate definition of the penumbra has been established, it will then be necessary to perform intervention studies to establish whether this tissue is salvageable or merely a scientific curiosity.

Factors contributing to the amount of damage in ischaemic tissue

Although the extent, and duration of reduction in CBF are probably the most important factors determining the area of ischaemic tissue, a number of other processes, occurring around the time of the initial insult or for days afterwards may be important but are not fully understood. Other examples of potential mediators of an ongoing ischaemic process are described below.

Animal studies have demonstrated that temperature changes of as little as two degrees can have a profound effect on the level of ischaemic damage; a rise in temperature having similar effects to an increased duration of ischaemia, and reducing temperature significantly reducing neuronal damage[31]. Hyperglycaemia post-stroke, after correcting for age, stroke severity and stroke sub-type, is associated with increased mortality and a poorer outcome[32]. One mechanism that is suggested for its negative effect is the exacerbation of ischaemia by the provoking of a 'spreading depression'-like increased oxygen demand in ischaemic tissue.

'Spreading depression' is the term used to describe the phenomenon seen in brain tissue of waves of depolarisation associated with an increased metabolic rate in the depolarised tissue, responding to the activation of energy-dependent ion pumps[25]. In the normal brain, the associated increase in demands for oxygen and glucose are coupled to an increase in CBF[33]. In ischaemia, glutamate-propagated intermittent waves of depolarisation, similar to spreading depression are seen. However, the consequent energy demands are not linked to an appropriate increase in CBF[34], and increases the burden on already compromised tissue.

It may be that neurones are less salvageable than initially suspected if an ischaemic insult triggers apoptosis, the term used to describe programmed cell death. It is distinct from cell necrosis, whereby cell membranes and mitochondria break down, with the

provocation of a potentially detrimental inflammatory response[35]. Features characteristic of apoptosis have been identified in ischaemic brain tissue, although it may just be that neuronal cell death demonstrates similar changes[36]. If apoptosis does occur however, the implication is that an ischaemic insult may continue to cause damage for a much longer time after the event than one would expect. Figure 4 gives a pictorial representation of the ongoing insults triggered by ischaemia that could continue to cause damage to affected tissue for up to days after the event.

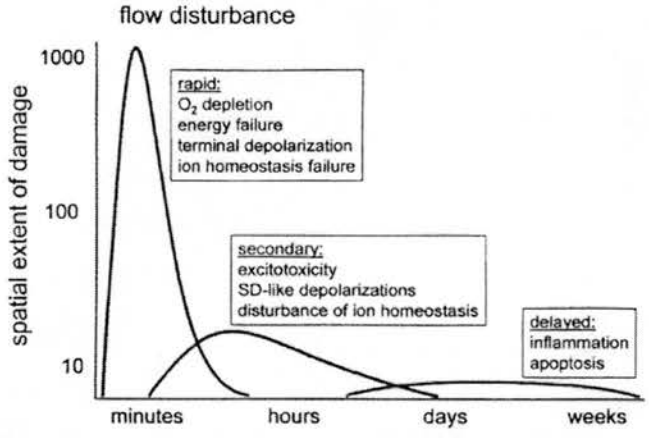


Figure 4. Hypothetical representation of extent and temporal course of development of ischaemic damage. (Reproduced from Weiss, 1999[29])

1.3.3 Intracerebral haemorrhage

When blood is extravasated through a critically weakened area of blood vessel it forms rounded haematoma. As the haematoma expands, further haemorrhage may be provoked as vessels surrounding it are compromised and rupture, producing a cascade of secondary haemorrhage and consequently ischaemia[37]. The haematoma either by virtue of its size, or combined with associated surrounding oedema may exert a significant mass effect on adjacent cerebral structures; kinking vessels, impeding cerebrospinal fluid flow and threatening vital functions.

At a cellular level, within minutes of the onset of bleeding, platelet aggregation occurs, clotting pathways are activated and clot is formed. The stabilisation of the clot by the cross-linkage of adjacent fibrin molecules causes it to retract, producing a heterogenous collection of erythrocytes and fibrin[38]. The fibrinolytic system will be activated, and

after a few days, red cell lysis occurs, initially at the centre of the haematoma. As oxygen levels drop within a haematoma, haemoglobin becomes deoxygenated to deoxyhaemaglobin, and breakdown products such as methaemoglobin appear.

Serial CT scanning of intracerebral haemorrhages demonstrate that a significant number of haematomas continue to expand for hours and sometimes days after onset of stroke[39;40]. Intracerebral haematomas are not static, uniform collections of blood, rather they are a heterogenous, dynamic entity. This heterogenous consistency, along with the changing concentrations of breakdown products of haemoglobin can make acute haemorrhage MRI difficult to interpret[41] (further details follow in this chapter and chapter 4).

1.4 The Clinical Examination And Its Limitations

Making a correct diagnosis of stroke is important

The diagnosis of stroke is made in patients who develop a clinical picture of rapid onset focal or global cerebral disturbance[42]. However, this is not always straightforward. There is no definition of the duration of time for 'rapid', symptoms vary widely and are not always focal (such as confusion or memory loss). Also, a wide range of conditions other than ischaemic stroke and ICH can cause identical stroke-like symptoms. 'Stroke mimics' such as brain tumours or cerebral infection have markedly different prognoses and their management is not the same as for stroke. Also, stroke due to vessel occlusion or ICH may present with identical symptoms making the two impossible to distinguish clinically. These issues will be discussed further in Chapter 2.

As our ability to treat conditions such as brain tumour improve, so it becomes important to distinguish such conditions from stroke. When no treatments of any proven benefit were available for stroke, identifying whether it was due to an ischaemic event or an ICH was relatively unimportant. However, when aspirin was demonstrated to be beneficial in ischaemic stroke for the prevention of death and stroke recurrence [43], with the recognition that anticoagulation prevents recurrent stroke in patients with atrial fibrillation, and with the advent of thrombolysis, which may be beneficial in ischaemic

stroke, the management of ischaemic stroke and ICH has diverged. In the near future, the management of patients with different levels of ischaemic damage may also vary. However, to instigate appropriate treatment, the clinician has to be able to identify the correct pathology.

The classification of stroke

Attempts have been made to define clinically important subgroups of ischaemic stroke. Two of the most commonly used examples are the Bamford[12] and the TOAST[44] classification (appendix I). The Bamford classification is based primarily on clinical findings and groups patients according to combinations of symptoms and signs; ischaemic strokes may be large or small, involve cerebral cortex (cortical) or small areas of deep structures (lacunar). Bamford classifications correspond with the site and size of their lesion in the brain, from which underlying aetiology can be inferred and outcome predicted. The TOAST classification[44] combines the results of neuroimaging, echocardiography and carotid Doppler ultrasound with clinical symptoms in an attempt to determine the precise aetiology of the stroke. Which classification is used depends on clinician preference and the context in which its use is being considered. For example, the TOAST classification would not be useful if access to diagnostic facilities are limited, or in the hyperacute situation when rapid diagnosis is the aim.

The need for neuroimaging

Currently, the diagnosis of stroke is still based on the judgment of a clinician confronted with a patient with certain combinations of symptoms and signs. There are a number of diagnostic aids that may be available to help the clinician feel more confident in their diagnosis. Autopsy may be a 'gold standard' of diagnosis but would only confirm diagnosis in those with the most severe strokes who die, not the more mild strokes who do not die until years later. One of the best diagnostic methods is monitoring clinical progress with time, as the clinical features of other conditions (such as tumours) become manifest, or other investigations confirm or exclude differential diagnoses. Neuroimaging with CT or MRI can improve and speed up the diagnostic process,

sometimes excluding important differentials immediately, or actually confirming stroke diagnosis.

Currently, most stroke physicians are constrained in their choice of imaging modality for patients with stroke to CT, although access to MRI is increasing[45]. As the number of neuroimaging techniques available to the stroke physician increases, so it becomes increasingly important to know the sensitivity (the proportion of patients who truly have the condition that is identified on imaging) and specificity (the proportion of patients who truly do not have the condition that is not identified on imaging) of each. This allows the clinician then to select the most appropriate technique for a given situation. This will be dealt with further in later chapters. Also, to derive the maximum information available from an image, it is helpful to understand how it was derived. The following section describes the principles of CT and MRI.

1.5 Principles Of Computerized Tomography And Magnetic Resonance Imaging

1.5.1 Computerised tomography (CT)

Development of CT

Computerized tomography was first described by Hounsfield in 1973[46], for which he was awarded the Nobel Prize. Its value in the differentiation of causes of stroke was rapidly realised[47]; one exploratory case series found positive findings in all 66 patients with intracerebral haemorrhage, and in 50% of those with ischaemic stroke[48]. Another series of patients clinically diagnosed as having cerebrovascular disease found that in those with a permanent neurological deficit, there was a corresponding lesion on CT in 57/58 (98%). In patients with transient neurological symptoms only 2/32 (6%) had an abnormality on CT, and that 43% of patients with haemorrhage on CT had had a clinical diagnosis of ischaemic stroke[49].

Principles of CT

To create an image using CT, a narrow beam of X-rays is passed through slices of the body part under investigation from multiple angles, and is attenuated to varying degrees depending upon the density (atomic number) of tissue it passes through. The beam is detected by sensing devices always pointed at the X-ray source. Information from multiple overlapping sources is then digitised and a two-dimensional image is constructed from thousands of data bits (pixels), the brightness of each bit being proportional to the degree of X-ray absorption[46]. Tissue contrast (a result of varying X-ray attenuation) is measured in Hounsfield Units (HU), and is proportional to the electron density, specific gravity or tissue water content of the tissue. For example, a 1% increase in tissue water content causes a decrease in attenuation of 2.5 HU, which will be manifest as an area that is hypodense compared to tissue with lower water content on imaging[50]. As scanners have evolved, the quality of image has improved as pixel size has decreased, and scan time has diminished to the point where a current spiral scanner can produce a set of images of the whole brain in as little as 20 seconds.

1.5.2 Magnetic resonance imaging (MRI)

Development of MRI

MRI is a spectroscopic technique based on the principles of nuclear magnetic resonance. This phenomenon was first described by Bloch and Purcell in 1946, both of whom received the Nobel Prize in 1952. MRI was initially developed for chemical and physical molecular analysis, but the idea of using it to detect disease within the human body began to gain ground in 1971, when it was demonstrated that tumour and normal tissue had different MRI properties ('relaxation times')[51]. In 1975 Richard Ernst proposed a new method of performing and analysing MRI which formed the basis of current MRI techniques[52], and in 1977 whole body MRI was first demonstrated[53].

The principles of MRI

Magnetic resonance imaging (MRI) makes use of the phenomenon of nuclear magnetic resonance; certain atomic nuclei, when placed in a magnetic field and stimulated by radio waves of a particular frequency, absorb energy that they re-emit as radio signals when the stimulation is switched off. Nuclear magnetic resonance occurs in atoms with nuclei that contain an odd number of neutrons or protons (known collectively as nucleons). Each nucleon has an intrinsic angular momentum, or 'spin', that generates a magnetic field; paired protons and neutrons align in such a way that their spins cancel out. Each nucleus thus behaves like a tiny bar magnet and normally they are orientated at random. If the nuclei are placed within a magnetic field however, they will be reorientated to become aligned with the applied field. Then, when a short radiofrequency (RF) pulse is applied via a coil surrounding the sample, it produces a second smaller magnetic field which will cause some of the aligned nuclei to experience a torque which will displace the axis of the net nuclear magnetization vector from its position parallel to the static field (figure 5). How much the axis is displaced depends upon the strength and duration of the RF pulse.

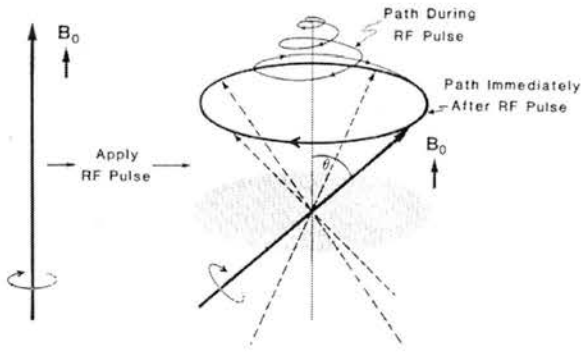


Figure 5. When a radiofrequency (RF) pulse is applied across a static magnetic field (B_o), the net magnetic moment is perturbed from its equilibrium position, the angle (θ) increasing as long as the pulse remains on. When the pulse is turned off, the vector gradually returns to its original position, its rotation describing the wall of a cone as it does so (adapted from Pykett 1982[54]).

When the RF pulse is turned off, the magnetization vector returns to its position parallel to the applied magnetic field, emitting a RF frequency signal that gradually diminishes. This phenomenon is characterised by two sample-related time constants, known as 'relaxation times' (termed T1 and T2). The image derived from the decaying signal may be a function of T1, T2 or both relaxation times, as well as the proton density of the sample. The extent to which each parameter contributes to image contrast depends upon the specific RF pulse sequence used[54].

The most biologically important nucleus in terms of imaging the human body is ^{1}H, as the body is made up primarily of water and fat, both rich in hydrogen. Other NMR-sensitive nuclei include ^{23}Na, ^{13}C and ^{31}P, although their lower biological concentrations make them less useful. As experience with MRI has progressed, the imaging characteristics of normal and diseased tissue using different pulse sequences have been identified. Certain sequences have proved more useful in the identification of certain tissues or disease states and these will be discussed further.

1.6 Pathological Changes Seen On Neuroimaging

1.6.1 Ischaemic stroke

Ischaemia on CT

The quality of image produced by early CT scanners made positive identification of ischaemia difficult[55], but with increasing sophistication, scanners can demonstrate signs of ischaemia within a few hours of stroke, although the signs may be subtle. Normal grey and white matter differ in their water and fat content; grey matter is relatively hyperdense with respect to white matter. In acute ischaemia, water moves into cells, and the subtle differentiation between grey and white matter can be lost. If the lesion is in the basal ganglia, there may be loss of outline of the lentiform nucleus and insular ribbon[56-59], if cortex is affected, there may be loss of grey/white cortex differentiation and swelling resulting in effacement of cortical sulci[60] (figure 6).

Figure 6. CT showing infarction (area of hypodensity) in the left parietal cortex (arrow)

As the infarct becomes more established, both grey and white matter become increasingly hypodense and lesions can become more obvious, although if small (e.g. lacunar strokes) can still remain difficult to identify[61;62]. Infarcts of the middle cerebral artery territory may be associated with a 'hyperdense middle cerebral artery sign' (HMCAS) as distal occlusion causes reduced blood flow or stasis within the vessel provoking clot formation. It has been noted in between 27[63] and 50%[64] of patients scanned within four to 12 hours respectively of MCA territory stroke (figure 7).

Figure 7. Hyperdense middle cerebral artery sign (HCMAS) (arrow)

As the infarct matures, by two to three weeks post ictus the previously hypodense lesion can become far less conspicuous i.e. more isodense with normal brain and less swollen, so-called 'fogging'[65], due to the infiltration of the infarcted tissue with macrophages, and the seepage of proteins and erythrocytes into the area. As the infarct matures, it may leave a sharply demarcated, shrunken area of roughly equivalent density to cerebrospinal fluid (CSF) that will be hypodense on CT. Adjacent structures such as cerebral ventricles may dilate as the area of infarction shrinks.

Ischaemia on MRI

On MRI, the tissue oedema produced by acute stroke results in hypointensity on T1-weighted images, and hyperintensity on T2-weighted and proton density images (figure 8). Changes may be demonstrated on T1 and T2 sequences within six hours of stroke[66], but this may not always be the case[67]. A more specialised FLAIR (fluid attenuated inversion recovery) sequence may demonstrate changes at an earlier time-point[68], as can diffusion-weighted imaging (see chapters 7 and 8). The normal signal flow void in the

supply artery may be lost if there is sluggish or stationary blood flow in a visible artery[69], which is the equivalent of the HMCAS on CT. As infarcts mature after several weeks, leaving an area of reduced brain mass, the lesion is bright on T2 and dark on T1 like CSF.

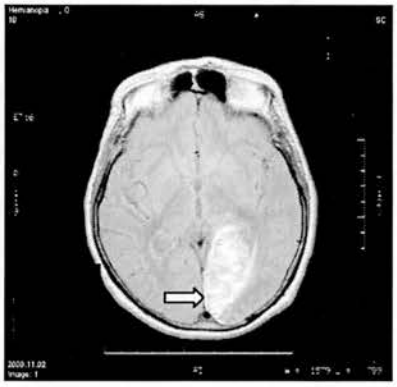


Figure 8. Ischaemia on MRI – Proton density sequence, hyperintensity in left occipital region (arrow) associated with swelling causing the occipital pole of the left lateral ventricle to be pushed forward

1.6.2 Intracerebral haemorrhage

Haemorrhage on CT

Haematoma has a specific gravity greater than that of water and consequently appears on CT as an area of high density or whiteness (about 80 HU compared with 35 HU for normal brain, figure 9). It appears rapidly after onset of symptoms[70] i.e. virtually instantaneously, is usually homogenous in intensity and surrounded by a varying area of lower attenuation (due to tissue oedema or necrosis)[60]. Extensive haematomas may be associated with intraventricular blood and behave as space-occupying lesions, provoking shifts in brain. As the haematoma resolves over days to weeks depending upon its size, the corresponding area of high density reduces until it becomes isodense with the surrounding brain tissue making recognition of previous haemorrhage unreliable at this time[71]. The time it takes for a haematoma to become isodense varies, with small haemorrhages disappearing in a matter of days[72]. As the affected area organises over weeks and months, there may be no residual signs, or only an area of non-specific focal atrophy with the low density of a CSF-containing cavity indistinguishable from old

ischaemic stroke, small patches of focal calcification, or a slit-like lesion usually only found following deep haemorrhages[73].

Figure 9. Haemorrhage on CT, haematoma demonstrated as area of hyperdensity (arrow) producing mass effect

Haemorrhage on MRI

The changes seen following brain haemorrhage on MRI are determined by the relative concentrations of haemoglobin, oxyhaemoglobin, deoxyhaemoglobin, methaemoglobin and haemosiderin. Deoxyhaemoglobin and methaemoglobin are paramagnetic, which makes them capable of exerting a magnetic susceptibility effect that alters T1 and T2 relaxation times. Acute haemorrhage contains high quantities of oxyhaemoglobin, which is not paramagnetic, consequently there may be little change in signal, or any changes may be indistinguishable from an ischaemic lesion[60]. As the breakdown product methaemoglobin is formed, the T1 image becomes hyperintense and the T2 image hypointense (figure 10)[74]. As the haematoma liquifies, the T2 image also becomes bright, and after a few weeks images will be bright in the centre surrounded by a dark rim seen more strikingly on T2 than T1 due to the persistence in brain tissue of haemosiderin, a breakdown product of haemoglobin[75].

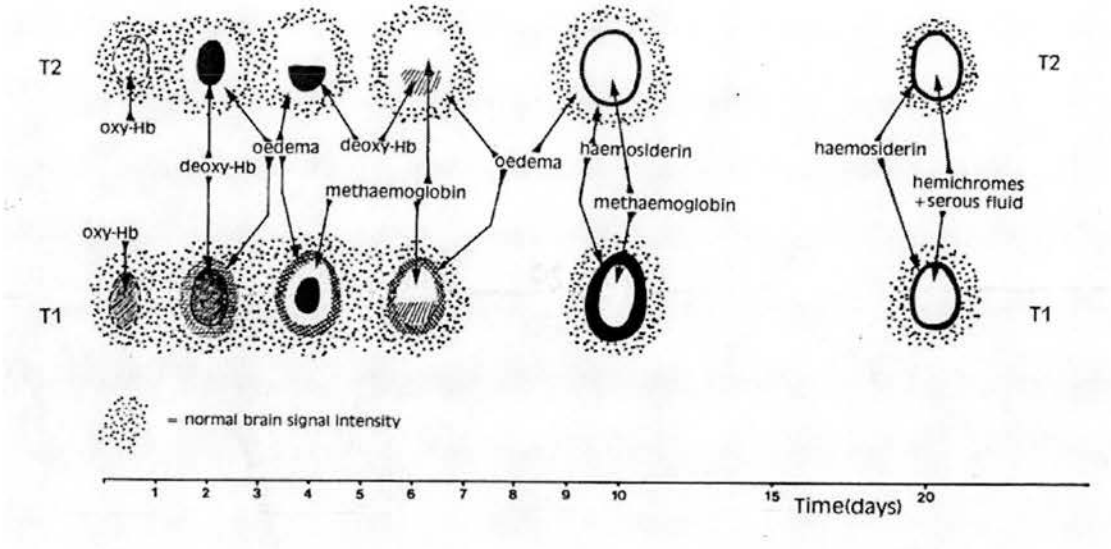


Figure 10. The evolution of haematoma seen on T1 and T2 imaging (adapted from Warlow et al 2000[60])

T2-weighted techniques introduced within the last few years that speed up image acquisition whilst maintaining image contrast and resolution (Fast Spin-Echo, FSE), have become the technique of choice in many institutions. However, there has been debate as to its sensitivity in the detection of haemorrhage[76]. Another specialised sequence (Gradient-Echo, GRE) has been shown to be particularly sensitive in the detection of haemorrhage[77] (figure 11). The relative merits of these sequences will be explored further in chapter 5.

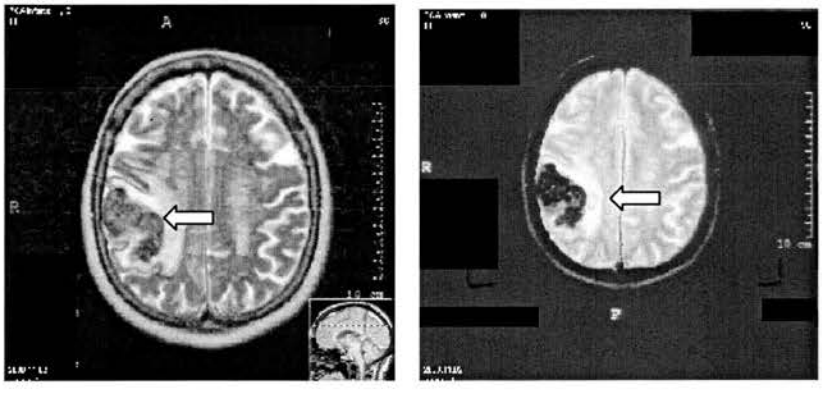


Figure 11. Haemorrhage on MRI. Left picture: T2 sequence – area of relative hypointensity right parietal region (arrow). Right picture: gradient echo sequence – note more marked hypointensity in affected region (arrow)

1.6.3 Haemorrhagic transformation

A certain proportion of ischaemic strokes will undergo haemorrhagic transformation (HTI). The exact frequency with which this occurs is unclear, as how often it is found depends upon the timing and frequency of scanning. In one study in which patients underwent repeated scanning, it was found that a proportion of ischaemic strokes had developed haematomas radiologically indistinguishable from PICH[78]. This raises the concerns that if patients are not scanned immediately upon presentation, a proportion may be incorrectly labelled as having PICH, and HTI may be missed if patients are not scanned repeatedly. The mechanism of HTI is also unclear; post-mortem studies in the 1950s suggested that the primary cause was reperfusion of damaged vessels following the break-up of an occluding embolus[79]. However, animal studies from around the same time observed that HTI was more severe if occluded vessels did not re-open, due to the leaking of vessels around the periphery of the infarct[80].

HTI is usually distinguished from a PICH by the lack of homogeneity of the haemorrhagic area, which appears within or on the edge of a presumed infarct. On CT, these patchy areas of increased density throughout an infarct (figure 12) can be confused with islands of surviving brain tissue can give a similar picture to the naked eye. The two can be distinguished by measuring the density in Hounsfield Units of the relevant areas on the CT console[60]. Very early HTI can be difficult to distinguish on MRI, but it becomes more apparent as more obvious paramagnetic breakdown products appear (figure 12).

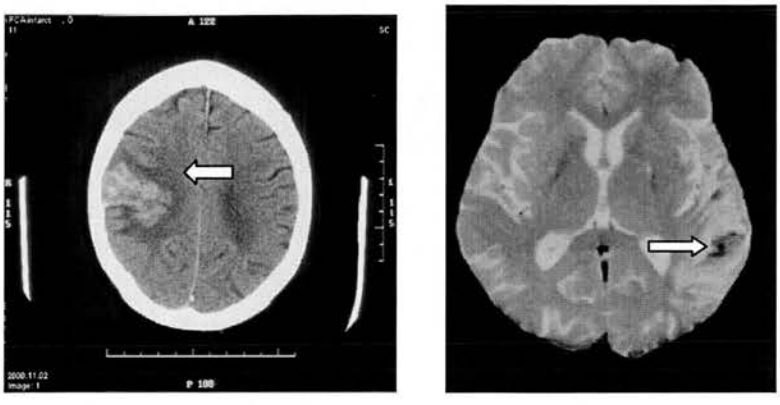


Figure 12. Haemorrhagic transformation. Left: CT showing a heterogenous area of hyperdensity surrounded by hypodense oedema (arrow). Right: MRI gradient echo sequence, showing irregular area of hypointensity surrounded by relative hyperintensity (arrow)

1.7 Summary

The brain is a demanding organ; its high metabolic rate means that it commands a disproportionate amount of cardiac output in relation to its size and its reliance on glucose metabolism renders it uniquely vulnerable to fluctuations in energy supply. These fluctuations however, can be compensated for, with some degree of success by cerebral autoregulation (altering CBF and CBV) and varying the OEF. Tissue ischaemia occurs when these compensatory processes are overwhelmed, setting in motion a vast array of molecular responses that continue for days after the initial event. Brain ischaemia is a dynamic process; the final degree of tissue damage being determined not only by the extent of reduction in CBF, but also the length of time over which it occurs and the ongoing molecular environment. Similarly, intracerebral haemorrhage is not a static event, but a dynamic process that evolves and regresses over days and weeks.

The clinical signs and symptoms produced by a stroke can be readily identified by clinicians, but are not specific enough to allow a very accurate diagnosis, either of stroke versus non-stroke, or ischaemic stroke as opposed to intracerebral haemorrhage. Neuroimaging with either CT or MRI improves the accuracy of diagnosis. Ischaemic stroke and intracerebral haemorrhage produce changes on imaging that evolve with time, and which become more or less easy to distinguish from normal brain tissue and each other depending upon the method and timing of scanning.

1. Hatano, S. Experience from a multicentre stroke register: a preliminary report. 54, 541-553. 1976. Bull World Health Org.

2. Clarke E. Apoplexy in the Hippocratic writings. Bulletin of the History of Medicine 1963;37:301-14.

3. Sudlow CLM,.Warlow CP. Comparable studies of the incidence of stroke and its pathological types. Results from an international collaboration. Stroke 1997;28:491-9.

4. Secretary of State for Health. Health of the Nation. 1992. London, HMSO.

5. Martin J., Meltzer H, and Elliot D. The prevalence of disability among adults. 1988. London, HMSO.

6. Waxman SG. Vascularization. In Butler J, Lebowitz H, eds. Correlative neuroanatomy, pp 168-87. New York: McGraw/Hill, 2000.

7. Hacke W, Hennerici M, Gelmers HJ, Kramer G. Applied anatomy of the cerebral arteries. In Hacke W, Hennerici M, Gelmers HJ, Kramer G, eds. Cerebral ischaemia, pp 1-16. Berlin: Springer-Verlag, 1989.

8. Cinnamon J, Viroslav AB, Dorey JH. CT and MRI diagnosis of cerebrovascular disease: going beyond the pixels. Seminars in Ultrasound, CT & MR 1995;16:212-36.

9. Jacobs MA, Knight RA, Soltanian-Zadeh H, Zheng ZG, Goussev AV, Peck DJ et al. Unsupervised segmentation of multiparameter MRI in experimental cerebral ischemia with comparison to T2, diffusion, and ADC MRI parameters and histopathological validation. J.Magn Reson.Imaging 2000;11:425-37.

10. van der Zwan A, Hillen B, Tulleken AF, Dujovny M, Dragovic L. Variability of the territories of the major cerebral arteries. J Neurosurg 1992;77:927-40.

11. Brott T, Adams HP, Olinger CP, Marler JR, Barsan WG. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864-70.

12. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991;337:1521-6.

13. Kase CS, Caplan LR. Intracerebral haemorrhage. In Newton MA, ed. Butterworth-Heinemann, 1994.

14. Warlow CP, Dennis MS, van Gijn J, Hankey GJ, Sandercock PAG, Bamford JM et al. What caused this intracerebral haemorrhage? Stroke: a practical guide to management, pp 339-75. Oxford: Blackwell Scientific Ltd, 2001.

15. Siesjo BK. Pathophysiology and treatment of focal cerebral ischemia. Part I: pathophysiology. J Neurosurg 1992;77:169-84.

16. Kety SS. Circulation and metabolism of the human brain ini health and disease. Am J Med 1950;8:205-17.

17. Leenders KL, Perani D, Lammertsma AA, Heather JD, Buckingham P, Healy MJ et al. Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age. Brain 1990;113 (Pt 1):27-47.

18. Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. Ann.Neurol. 1991;29:231-40.

19. Powers WJ. Acute hypertension after stroke: the scientific basis for treatment decisions. Neurology 1993;43:461-7.

20. Pulsinelli W. Pathophysiology of acute ischaemic stroke. Lancet 1992;339:533-6.

21. Matsuoka Y,.Hossmann KA. Brain tissue osmolality after middle cerebral artery occlusion in cats. Exp.Neurol. 1982;77:599-611.

22. Fisher M. Characterizing the target of acute stroke therapy. Stroke 1997;28:866-72.

23. Sharborough FW, Messick JM, Sundt TM. Correlation of continouos electroencephalograms with cerebral blood flow measurement during carotid endarterectomy. Stroke 1973;4:674-83.

24. Astrup J, Symon L, Branston NM, Lassen NA. Cortical evoked potential and extracellular K+ and H+ at critical levels of brain ischemia. Stroke 1977;8:51-7.

25. Hossman KA. Viability thresholds and the penumbra of focal ischemia. Ann Neurol 1994;36:557-65.

26. Jones TH, Morawetz RB, Crowell RM, Marcoux FW, FitzGibbon SJ, DeGirolami U et al. Thresholds of focal cerebral ischemia in awake monkeys. J.Neurosurg. 1981;54:773-82.

27. Baron JC. Mapping the ischaemic penumbra with PET: implications for acute stroke treatment. Cerebrovasc Dis 1999;9:193-201.

28. Furlan M, Marchal G, Viader F, Derlon JM, Baron JC. Spontaneous neurological recovery after stroke and the fate of the ischemic penumbra [see comments]. Ann Neurol 1996;40:216-26.

29. Heiss WD, Thiel A, Grond M, Graf R. Which targets are relevant for therapy of acute ischemic stroke? Stroke 1999;30:1486-9.

30. Ginsberg MD. Delayed OEF elevation is an unreliable index of tissue at risk. Ann Neurol 1997;41:411-22.

31. Minamisawa H, Smith ML, Siesjo BK. The effect of mild hyperthermia and hypothermia on brain damage following 5, 10 and 15 minutes of forebrain ischaemia. Ann Neurol 1990;26-33.

32. Weir CJ, Murray GD, Dyker AG, Lees KR. Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long-term follow up study. BMJ 1997;314:1303-6.

33. Kocher M. Metabolic and hemodynamic activation of postischaemic rat brain by cortical spreading depression. Journal of Cerebral Blood Flow & Metabolism 1990;10:564-71.

34. Nedergaard M,.Astrup J. Infarct rim: effect of hyperglycemia on direct current potential and C14-deoxglucose phosphorylation. Journal of Cerebral Blood Flow & Metabolism 1986;6:607-15.

35. Kuschinsky W,.Gillardon F. Apoptosis and cerebral ischaemia. Cerebrovasc Dis 2000;110:165-9.

36. MacManus JP,.Linnik MD. Gene expression induced by cerebral ischemia: an apoptotic perspective. J.Cereb.Blood Flow Metab 1997;17:815-32.

37. Fisher CM. Pathological observations in hypertensive cerebral haemorrhage. J Neuropathology and Experimental Neurology 1971;30:536-50.

38. Taber KH, Hayman LA, Herrick RC, Kirkpatrick JB. Importance of clot structure in gradient-echo magnetic resonance imaging of hematoma. JMRI 1996;6:878-83.

39. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. Stroke 1996;27:1783-7.

40. Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki O. Hematoma enlargement in spontaneous intracerebral hemorrhage. J Neurosurg 1994;80:(pp 51-7).

41. Hayman LA, Pagani JJ, Kirkpatrick JB, Hinck VC. Pathophysiology of acute intracerebral and subarachnoid hemorrhage: Applications to MR imaging. American Journal of Roentgenology 1989;153:135-9.

42. Hatano, S. Experience from a multicentre stroke register: a preliminary report. 54, 541-553. 1976. Bull World Health Org.

43. Chen ZM, Sandercock P, Pan HC, Counsell C, Collins R, Liu LS et al. Indications for early aspirin use in acute ischemic stroke : A combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. Stroke 2000;31:1240-9.

44. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.

45. Ebrahim, S. and Redfern, J. Stroke Care - a matter of chance. A national survey of stroke services. 1999. London, The Stroke Association.

46. Hounsfield GN. Computerized transverse axial scanning (tomography). 1. Description of system. Br.J.Radiol. 1973;46:1016-22.

47. Ambrose J. Computerised transverse axial scanning (tomography): part 2: clinical application. Br.J.Radiol. 1973;46:1023-47.

48. Paxton R,.Ambrose J. EMI scanner: brief review of first 650 patients. Br.J.Radiol. 1974;47:530-65.

49. Kinkel WR,.Jacobs L. Computerized axial transverse tomography in cerebrovascular disease. Neurology 1976;26:924-30.

50. Unger E, Littlefield J, Gado M. Water content and water structure in CT and MR signal changes: possible influence in detection of early stroke. Am J Neuroradiol 1988;9:687-91.

51. Damadian R. Tumor detection by nuclear magnetic resonance. Science 1971;171:1151-3.

52. Kumar A, Welti D, Ernst R. NMR Fourier Zeugmatography. J Magnetic Resonance 1975;18:69-83.

53. Damadian R, Minkoff L, Goldsmith M. Whole-body nuclear magnetic resonance scanning: n.m.r. studies of tumour cells. Ciba Found.Symp. 1978;131-41.

54. Pykett IL, Newhouse JH, Buonanno FS, Brady TJ, Goldman MR, Kistler JP et al. Principles of Nuclear Magnetic Resonance Imaging. Radiology 1982;143:157-68.

55. Campbell JK, Houser OW, Stevens JC, Wahner HW, Baker HL, Jr., Folger WN. Computed tomography and radionuclide imaging in the evaluation of ischemic stroke. Radiology 1978;126:695-702.

56. Tomura N, Uemura K, Inugami A, Fujita H, Higano S, Shishido F. Early CT finding in cerebral infarction:obscuration of the lentiform nucleus. Radiology 1988;`168:463-7.

57. Truwit CL, Barkovich AJ, Gean-Marton A, Hibri N, Norman D. Loss of the insuar ribbon: another early CT sign of acute middle cerebral artery infarction. Radiology 1990;176:801-6.

58. Grond M, von Kummer R, Sobesky J, Schmulling S, Rudolf J, Terstegge K et al. Early Xray hypoattenuation of brain parenchyma indicates extended critical hypoperfusion in acute stroke. Stroke 2000;31:133-9.

59. von Kummer R, Allen KL, Holle R, Bozzao L, Bastianello S, Manelfe C et al. Acute stroke: usefulness of early CT findings before thrombolytic therapy [see comments]. Radiology 1997;205:327-33.

60. Warlow CP, Dennis MS, van Gijn J, Hankey GJ, Sandercock PAG, Bamford JM et al. What pathological type of stroke is it? Stroke: a practical guide to management, pp 151-222. Oxford: Blackwell Scientific Ltd, 2001.

61. Donnan GA, Tress BM, Bladin PF. A prospective study of lacunar infarction using computerized tomography. Neurology 1982;32:49-56.

62. Bamford J, Sandercock P, Jones L, Warlow C. The natural history of lacunar infarction: the Oxfordshire Community Stroke Project. Stroke 1987;18:545-51.

63. Bastianello S, Pierallini A, Colonnese C, Brughitta G, Angeloni U, Antonelli M et al. Hyperdense middle cerebral artery CT sign. Comparison with angiography in the acute phase of ischemic supratentorial infarction. Neuroradiology 1991;33:207-11.

64. Leys D, Pruvo JP, Godefroy O, Rondepierre P, Leclerc X. Prevalence and significance of hyperdense middle cerebral artery in acute stroke. Stroke 1992;23:317-24.

65. Becker H, Desch H, Hacker H, etal. CT fogging effect with ischemic cerebral infarcts. Neuroradiology 1979;18:185-92.

66. Hasso AN, Stringer WA, Brown KD. Cerebral ischaemia and infarction. Neuroimaging Clinics of North America 1994;4:733-52.

67. Yuh WTC, Crain MR, Loes DJ, Greene GM, Ryals TJ, Sato Y. MR imaging of cerebral ischaemia: findings in the first 24 hours. Am J Neuroradiol 1991;12:621-9.

68. Noguchi K, Ogawa T, Inugami A, Fujita H, Hatazawa J, Shimosegawa E et al. MRI of acute cerebral infarction: a comparison of FLAIR and T2-weighted fast spin-echo imaging. Neuroradiology 1997;39:406-10.

69. Cinnamon J, Viroslav AB, Dorey JH. CT and MRI diagnosis of cerebrovascular disease: going beyond the pixels. Seminars in Ultrasound, CT & MR 1995;16:212-36.

70. Franke FL, Ramos LMP, van Gijn J. Development of multifocal haemorrhage in a cerebral infarct during computed tomography. J Neurol Neurosurg Psychiatr 1990;53:531-2.

71. Dennis MS, Bamford JM, Molyneux AJ, Warlow CP. Rapid resolution of signs of primary intracerebral haemorrhage in computed tomograms of the brain. BMJ 1987;295:379-81.

72. Hung TP,.Lee KY. Small intracerebral haemorrhage: a study of clinical manifestations and CT findings on 31 cases. Annals of the Academy of Medicine, Singapore 1985;14:22-31.

73. Franke CL, van Swieten JC, van Gijn J. Residual lesions on computed tomography after intracerebral hemorrhage. Stroke 1991;22:1530-3.

74. Edelman RR, Johnson K, Buxton R, Shoukimas G, Rosen KR, Davis KR. MR of hemorrhage: a new approach. Am J Neuroradiol 1986;7:751-6.

75. Gomori JM, Grossman RI, Goldberg HI, Zimmerman RA, Bilaniuk LT. Intracranial hematomas: imaging by high-field MR. Radiology 1985;157:87-93.

76. Jones KM, Mulkern RV, Mantello MT, Melki PS, Ahn SS, Barnes PD et al. Brain hemorrhage: evaluation with fast spin-echo and conventional dual spin-echo images. Radiology 1992;182:53-8.

77. Melhem ER, Patel RT, Whitehead RE, Bhatia RG, Rockwell DT, Jara H. MR imaging of hemorrhagic brain lesions: a comparison of dual- echo gradient- and spin-echo and fast spin-echo techniques. AJR 1998:797-802.

78. Bogousslavsky J, Regli F, Uske A, Maeder P. Early spontaneous hematoma in cerebral infarct: is primary cerebral hemorrhage overdiagnosed? Neurology 1991;41:837-40.

79. Fisher M,.Adams RD. Observations on brain embolism with special reference to the mechanism of haemorrhagic infarction. J Neuropathology and Experimental Neurology 1951;10:92-4.

80. Globus JH,.Epstein JA. Massive cerebral haemorrhage: spontaneous and experimentally induced. J Neuropathology and Experimental Neurology 1953;12:107-31.

2 The Importance Of Neuroimaging In Making An Accurate Diagnosis In Patients With Stroke Symptoms

2.1 Introduction

Conditions other than stroke can present with stroke-like symptoms

There are a number of intracerebral conditions that can present with symptoms similar or identical to those seen in stroke. Tumour, encephalitis, abscess, demyelination or degeneration can all provoke focal signs that can be difficult to distinguish from ischaemia. Certain symptoms or signs, such as memory loss may imply a focal cerebral impairment but can be caused by diffuse cerebral dysfunction. Even lesions outside the brain such as vestibulitis or extra-ocular muscle dysfunction can confuse. Differentiating such conditions from a stroke on clinical examination can be difficult.

Accurate determination of the pathological cause of stroke requires neuroimaging

Distinguishing the pathological cause of stroke (i.e. ischaemic stroke or intracerebral haemorrhage, ICH) on clinical judgement alone is also difficult. Typical but not specific features of ICH such as headache, vomiting, early sedation and reduced consciousness tend to reflect a rapid rise in intracranial pressure and are associated with large haemorrhages. Cerebral infarction may cause similar symptoms and signs, and smaller haemorrhages may have none of these symptoms. One study of a hospital population found the initial bedside diagnosis of physicians to be accurate in only 69% of cases examined[1]. To aid the clinician in the distinction of ICH, scoring systems were developed. These made use of the presence or absence of factors found to be associated with patients with known ICH. Two of the most well known examples are the Allen probability guide (also known as Guy's Hospital Score)[2] and Siriraj[3] score (appendix II), and are an improvement on clinical judgement alone. Using the Allen guide improved clinician's accuracy in correctly distinguishing ischaemic stroke from ICH from 84% to 90%[2]. The sensitivity of a Siriraj score of greater than one (for

diagnosis of ICH) was 89.3%[3]. However, these scores are much less accurate when used in a stroke population other than the one from which they were derived[4]. In one study, the sensitivity of the Allen Score (using a cut-off of greater than 24 to indicate a high likelihood of haemorrhage) dropped to 31% and the sensitivity of a Siriraj score of greater than one, to 48%[5]. The gold standard against which these scoring systems were compared when externally validated, was CT scanning.

The accuracy of these scores will have been compromised by the bias towards more severe stroke seen in the populations from which they were derived. Hospitalised patients were used, some of whom had their diagnosis confirmed at post mortem. As CT scanning has become more available, the frequency of minor ICH has increased[6], and with it the realisation that patients with ICH won't necessarily present with severe symptoms[4]. Therefore, for accurate determination of the cause of stroke, neuroimaging is required. However, because of the limited amount of time that haemorrhage is visible on CT (see chapter 1), it is vital to scan patients early after the stroke onset particularly to avoid overlooking small haemorrhages.

How accurate are epidemiological estimates for the incidence of ICH and ischaemic stroke?

Epidemiological studies of stroke incidence commonly attempt to determine the relative proportions of ischaemic stroke and ICH. The data accrued from such studies are then used in a wide range of Health Economics and research settings. There have been numerous studies of stroke incidence, both hospital and community-based. Hospital-based studies will provide an underestimate of incidence unless all patients with stroke are admitted, and it is not possible to be sure that all cases are admitted without looking in the community. Therefore, hospital-based studies cannot accurately measure incidence in a population. The International Stroke Incidence Collaboration identified comparable community incidence studies, mostly from the 1980's and early 1990's, and found that between 73 and 86% of strokes were due to ischaemic stroke, between 8 to 15% to ICH, and one to five percent to subarachnoid haemorrhage[7]. No attempt was made in these studies, to distinguish primary intracerebral haemorrhage from haemorrhagic transformation (HTI). It can be difficult to distinguish the two and their

relative frequency may vary depending upon timing of scanning[8]. Hospital admission rates varied considerably between included studies; in the Oxfordshire Community Stroke Project[9] (OCSP), the admission rate was 55%, whereas in SEPIVAC[10], in Italy the admission rate was 85%.

Some studies included an 'unknown' category for cases where the cause was uncertain, usually because the patient had not had a CT scan, or post mortem if they had died. The methods used in these studies to diagnose the cause of the stroke varied though all used brain CT scanning to some degree. However, the precise use of CT scanning (the proportion scanned, within what time interval), and the influence this might have had on the proportion of strokes diagnosed as ischaemic stroke or ICH has not been reviewed.

Systematic reviews of studies of the proportions of stroke mimics found in populations presenting with stroke symptoms, and the effect that scanning methods may have on the results of community-based stroke incidence studies

To investigate these issues further, I performed two systematic reviews:

- *To determine the potential proportion of non-strokes in a population presenting with stroke-like symptoms.* There are studies (with varying primary aims) that have documented the proportions of stroke mimics in populations of patients presenting with stroke symptoms. In general the gold standard by which the final diagnosis was made was neuroimaging. Some assessed the ability of different populations of clinicians, ranging from paramedics to neurologists, to be able to diagnose stroke accurately. These studies were analysed for the range of conditions that can mimic stroke, the proportions of a stroke population that they represent, and the relative importance of neurological training in making a stroke diagnosis.

- *To determine the effect of scanning methods on the results of community-based stroke incidence studies.* In order to determine the influence that neuroimaging may have had on the documented incidence of ICH and ischaemic stroke, I performed a systematic review of community-based studies that aimed to determine the incidence of stroke and its pathological subtype. The scanning methods in these studies were examined,

in order to analyse their impact upon the estimate of the proportion of all strokes due to ICH.

2.2 Methods

2.2.1 The proportion of stroke mimics in populations of patients presenting with stroke

Search strategy

In order to identify studies for both systematic reviews, electronic searches of the medical databases, MEDLINE and EMBASE were performed. To make the searches as inclusive as possible, an extended search strategy was used to identify articles relevant to stroke (appendix III). This strategy, pioneered by the Cochrane Collaboration Stroke Research Group[11] for the identification of randomised controlled trials, identifies more relevant references than a standard search that uses subject headings and specific text words. Although this strategy has not been used to identify observational studies, I used it as a starting point to maximise the number of references captured.

Data pertaining to the proportion of stroke mimics in a population were present in studies with differing primary purposes, so a number of searches were undertaken. In the electronic searches, title and text words for 'diagnosis' were added to the Cochrane Library extended stroke strategy. A separate search using title and text words for 'timing' and 'delay' was also performed, as studies pertaining to the timing of admission of patients with stroke symptoms to hospital, with reference to the potential delivery of hyperacute stroke treatment occasionally contained relevant data. Abstracts of conference proceedings concerned with time of arrival of patients with stroke symptoms to hospital were identified and followed-up. Stroke incidence studies identified for the review on scanning policies were also studied.

Inclusions

Studies of specific populations of patients presenting with stroke symptoms, that documented both the initial and final proportions of patients with the diagnosis of stroke (compared with non-stroke) and details of the nature of stroke mimics were included. Also included were studies that documented values for the final proportion of true strokes in a population presenting with stroke symptoms, and where it could be determined which health professional made the first clinical diagnosis were included.

Data extraction

Data were extracted on: the purpose and size of study, the profession of the person making the initial clinical diagnosis, the gold standard by which final diagnosis was made, the proportions of the study population with final diagnosis of non-stroke, ischaemic stroke or ICH, values for sensitivity and specificity of diagnosis of stroke compared to non-stroke, and ischaemic stroke compared to ICH. Data were analysed with simple descriptive statistics. The mean value for sensitivity of diagnosis for different health professionals was determined with 95% confidence intervals. The studies in which Emergency Physicians had access to CT results were not included in these calculations.

2.2.2 Scanning policies in stroke incidence studies

Search strategy

MEDLINE and EMBASE were searched from January 1980 to April 1999. To the Cochrane Library extended search strategy the following text words were added: 'stroke register, stroke registry, incidence, community' and subject heading 'incidence'. The electronic search went no further back than 1980 because, although CT was clinically available before this time, its use in community incidence studies was very limited. I also examined reference lists and had discussions with other interested investigators, including the International Stroke Incidence Collaboration.

Inclusions and exclusions

All community-based stroke incidence studies in which the actual proportion of ischaemic stroke and haemorrhage were reported were included. Hospital-based studies were excluded, as were studies that did not report the frequency of ICH separately from ischaemic stroke (i.e. just reported all 'stroke'), studies that documented either ICH or ischaemic stroke only, or case fatality data only.

Data extraction

Data were extracted on year of publication and sample size of each study, the method of diagnosing the pathological cause of stroke, use of scanning, the proportion with ischaemic stroke or ICH, and any information on patients not scanned. Data were entered into an Access database and analysed with descriptive statistics. Patients with subarachnoid haemorrhage were excluded from both the denominator and numerator, because although there may be patients with overlapping symptoms, this condition is generally distinct from stroke due to infarction or intracerebral haemorrhage.

2.3 Results

2.3.1 The proportion of stroke mimics in populations of patients presenting with stroke

Electronic searches captured 3794 references, and their abstracts were scanned for relevant studies. Seventeen studies were identified that included data on the proportion of stroke mimics in a population presenting with stroke (table 1). The total number of patients presenting with stroke symptoms was 9316, and the median study size was 411. The studies varied widely in their premise; seven (6228 patients) were stroke incidence studies, in which the primary aim was not to determine the accuracy of the referring clinician, rather to identify all strokes in a defined population [9;10;12-16]; seven (1982 patients) examined the accuracy of diagnosis of various professionals concerned in the management of patients with acute stroke[20;21;46-50]; three (1046 patients) were primarily

concerned with the process of acute stroke care delivery[17-19]. Only in studies concerning the accuracy of Emergency Physicians were CT results available at first point of contact[20;21]. Final diagnosis was made by a Neurologist or Physician with an interest in stroke in fourteen studies, and unspecified in the remaining three. The proportion of the study population that was eventually diagnosed as having a condition other than stroke varied from one to 49%. The conditions identified that could mimic stroke were numerous, the commonest conditions included intracerebral neoplasm (primary and secondary), infections and subdural haematoma (table 2).

Excluding stroke incidence studies, the mean sensitivities of stroke diagnosis for different groups of health professionals at first point of contact with the patient with stroke symptoms were as follows: paramedics 74.9% (95% CI 68.8-81.0%); General Practitioners 87.7% (95% CI 84.7-90.8); and Emergency Room personnel 71.1% (95% CI 68.6-73.6%).

2.3.2 Scanning policies in stroke incidence studies

Included studies

Electronic searching captured 1903 references, and their abstracts scanned for relevant studies. 49 studies were examined, 25 studies of which met the inclusion criteria (table 3). One included study specifically excluded subarachnoid haemorrhage[22]. 23 studies (92%) included a category where the cause of stroke was 'undetermined'. In 12/23 studies (48%), 'undetermined' referred only to patients who did not undergo postmortem or scanning at any time. In the remaining 11 studies, patients could be categorized as ischaemic stroke, ICH or 'undetermined' even if no scan or postmortem had been performed, i.e. they were classified on clinical judgement alone. This was also the case for the two studies[23;24] that classified all patients as either ischaemic stroke or ICH. Two studies used the Allen score as a diagnostic aid[10;25].

Documented details of scanning policies

In the included studies, the details of scanning rates, times of scanning and exclusions varied immensely; 5/25 (20%) studies gave no scanning details at all[26-30]. Of the 20 that did give details, the proportion of patients scanned (or who had a postmortem) varied from less than 30% to approaching 96% (figure 1). Although these 20 studies indicated the proportion of patients scanned, only 13/25 (52%) mentioned the time interval from onset of symptoms to CT scanning (figure 2). Information on timing of scanning was documented in a number of different ways; one study gave a value for the mean time interval from onset of symptoms to scanning for those patients who underwent neuroimaging[31], and two studies gave the median time interval from symptoms to scanning[14;32]. The majority of studies, documented the proportion of patients scanned within a certain time interval, ranging from seven days[24;33;34], to 21 days[35] and 30 days[10;12;15;16;25;36]. In no study was it explicit exactly what proportion of patients were scanned when (i.e. within one week, two weeks, three weeks after stroke) making it impossible to get a complete picture of the overall accuracy of the diagnosis of ischaemic or haemorrhagic stroke.

In the nine studies that provided the information, patients treated at home, those who died very early after their stroke, and the elderly were the groups most likely not to be scanned at all (table 4). In the few studies which specifically mentioned an age barrier, 'elderly' was greater than 75 years.

Figure 1. Stroke incidence studies ranked according to proportions of strokes scanned overall (point estimates of PICH with 95% confidence intervals). Note: scans may have been greater than two weeks from stroke onset (see figure 2 for timing).

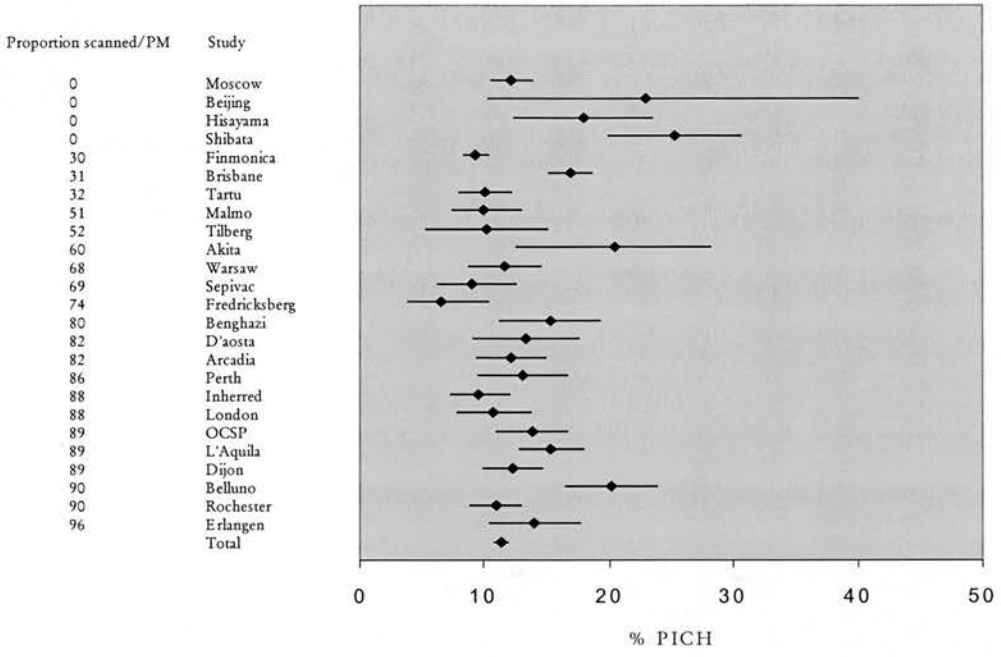
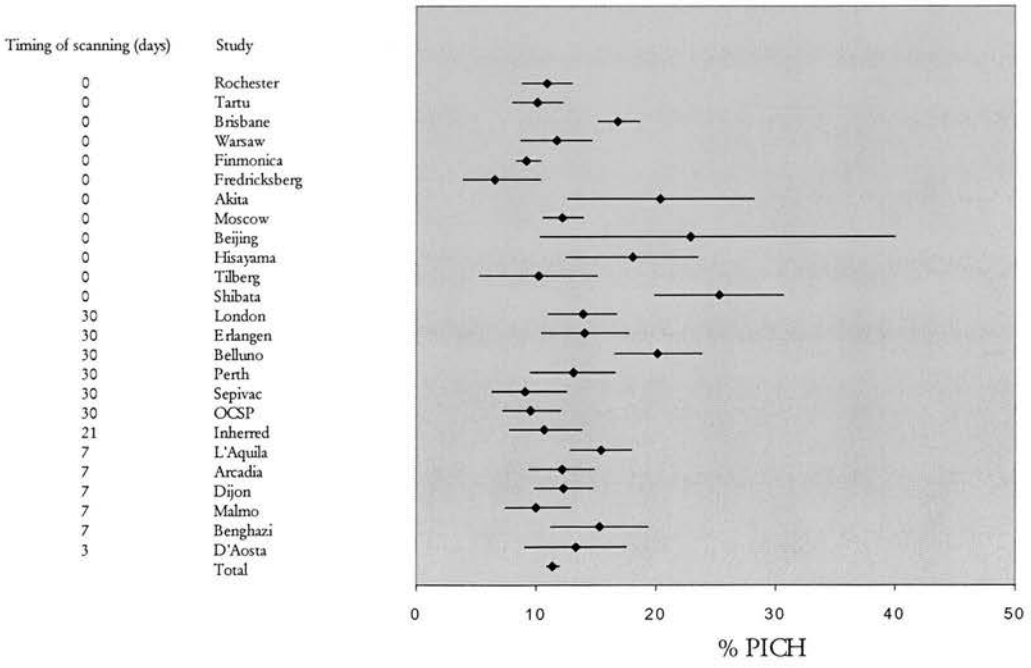


Figure 2. Stroke incidence studies ranked according to speed of scanning following onset of stroke symptoms (point estimates of PICH with 95% confidence intervals). Note: not all patients scanned (see figure 1 for proportion). '0' denotes no information on timing of scanning.



Estimation of the 'true' incidence of PICH

The proportions of subjects defined as having PICH varied widely. Also, it is very likely that some of the patients not scanned, or scanned late after stroke and were diagnosed as ischaemic stroke, actually had PICH. However, it was impossible to determine from the majority of studies how many patients this bias might have affected. Therefore, to attempt to estimate what effect any underdiagnosis of PICH might have had on the observed ratio of PICH/infarct, a 'best' and 'worst' case scenario was estimated. To do this, only studies that scanned more than 30% of patients were used. In the 'best' case scenario, it was assumed that no patients in the uncertain (i.e. unscanned) category had PICH and in the 'worst' case scenario that all patients in the uncertain category had PICH, as well as those actually classified as PICH. We calculated the mean proportions per study (best and worst) and 95% confidence intervals. The mean study sample size was 529 and the proportion of PICH ranged from an estimated 13 to 25% (95% CI, 10 -29%).

2.4 Discussion

Not everybody presenting with stroke symptoms is having a stroke

The primary purposes of studies including data on the proportion of stroke mimics found in a population of people presenting with stroke symptoms varied from documenting stroke incidence, to analysis of health professional accuracy, to examining stroke process. This variation may contribute to the wide range of values for proportion of stroke mimics reported. General physicians seemed to be better at making a correct diagnosis than paramedics and emergency room personnel, although confidence intervals were relatively wide. What these studies do highlight is that diagnosis by clinician alone, without a corroborative scan, will be incorrect a significant proportion of the time, and this proportion is less when scan results are available[20]. If (as with thrombolysis) time to presentation to the acute stroke team is important, who makes the first referral is relatively immaterial.

Scanning policies in stroke incidence studies are not comprehensive

No community-based study of stroke incidence achieved a 100% CT scan rate within a time-frame which would definitely allow distinction of PICH from ischaemic stroke (i.e. within one week, see chapter 5.3). In general, studies either scanned quickly enough but scanned relatively few patients, or scanned more patients but too late to identify ICH reliably. It is therefore very likely that the incidence of ICH has been underestimated, particularly the incidence of small haemorrhages, but there is no information to determine by what degree. Our 'best and worst' estimate gives some indication of the potential scale of the problem.

Why do scanning policies vary so widely?

These are community-based studies, some of which made exhaustive attempts to capture all people in the region under scrutiny who experienced stroke-like symptoms. Some studies were performed as far back as 1980, when being able to distinguish whether a stroke was caused by ischaemia or haemorrhage made no difference to the management of the patient. Access to CT for the investigation of stroke has improved with time, but not uniformly throughout the world and this paper includes studies where access is still difficult (although Western European studies have little excuse). Early, comprehensive scanning may be impractical or unaffordable, and post-mortem might be socially unacceptable. However, the fact remains that in those patients who did not undergo CT scanning within an appropriate time frame, or post-mortem, it is not possible to be unequivocally sure as to the pathological type of stroke.

Could it be that PICH is being overdiagnosed?

Very early haemorrhagic transformation (HTI) of a cerebral infarct can mimic ICH[8] but from the studies we reviewed there is no way of knowing how often this might have been the case. The cause of HTI is unclear, as is the prognosis of patients with HTI. Patients with HTI may respond differently to acute treatment and secondary prevention (with antithrombotic drugs or anticoagulants) than those with either ischaemic stroke or

ICH. Without more accurate categorisation of the condition by early scanning, it will be impossible to address these issues.

Bias in scanning policies

It is more likely that the proportion of stroke due to PICH is being underestimated rather than overestimated, due to late scanning, and the bias introduced by the conspicuous lack of scanning in those patients managed at home, dying early or the 'elderly'.

Patients with milder strokes may not be seen at hospital at all or not until many days or even weeks have passed, well beyond the time when CT can reliably differentiate haemorrhage from infarct. On the basis of existing evidence, these patients are generally considered less likely to have had a ICH than the more severe strokes that are admitted to hospital earlier[2;3], and are therefore managed as ischaemic strokes. This assumption may not be correct, as ICH can be detected in patients with very mild strokes, and even in patients with transient ischaemic attacks if scanned soon after symptom onset[37;6] (and chapter 5). Also, as the use of CT in stroke has increased, so has the incidence of smaller, more benign ICH[6].

From what we do know about the outcome of patients with ICH, albeit from studies that may have missed milder strokes, it seems that the more severe the stroke, the more likely it is to be haemorrhage[38]. Therefore, in patients with severe symptoms (too sick to scan), there may be an over-representation of ICH.

The median age for stroke to occur is 72 years, thus roughly half of all the strokes in a population may not have been scanned in incidence studies that failed to scan the elderly. The incidence of amyloid angiopathy, a risk factor for ICH, increases with age[39], and increasing use of magnetic resonance imaging has revealed that it is not uncommon to find evidence of old, apparently asymptomatic haemorrhages in the brains of elderly patients[40;41]. It may be that older people are particularly at risk of ICH, and thus there may be an over-representation of ICH in this group not being scanned in incidence

studies. One cannot assume that the proportion of ICH to ischaemic stroke remains constant across all ages.

Is scanning really necessary for population studies?

It is important to collect information on all strokes, especially in the developing world as there is so little information available. Therefore, in this context, you could argue not to bother with neuroimaging and just collect data on 'all strokes'. Accuracy could be augmented by the use of clinical scoring systems, which are at least better than clinical judgement alone in the diagnosis of severe strokes due to haemorrhage. However, in the developed world, where it is increasingly essential to distinguish infarct from haemorrhage, it seems inappropriate at the present time for any future incidence studies not to ensure that they use CT or MRI to determine the actual cause of stroke as precisely as possible across all age groups and severities of stroke.

Conclusion

Conditions that mimic stroke may have very different management strategies from true stroke. They are not uncommon, and clinicians will not identify them accurately all of the time. The advent of thrombolysis highlights the problem of increasingly sophisticated (and potentially dangerous) management strategies that demand levels of diagnostic accuracy that clinicians are not capable of achieving without neuroimaging.

On the evidence of community-based stroke incidence studies, ICH has probably been underdiagnosed especially in mild strokes, the elderly and those who died soon after the event. Comprehensive scanning in community-based studies is extremely difficult to achieve. There are real and practical hindrances to widespread early scanning and these issues continue to result in less than ideal scanning strategies[42-45]. However, because of the weakness of scanning policies, we cannot really be sure precisely what proportion of stroke in various countries is due to ICH rather than ischaemic stroke, and as a consequence, any research relying on data from them, such as that into the genetics of stroke, could be inherently flawed.

Table 1. Studies documenting data on the proportion of patients with a final diagnosis of non-stroke in populations presenting with stroke symptoms

Study	Date of publication	Size	Setting	Person making initial diagnosis of stroke	Proportion of patients with non-stroke as final diagnosis (%)
OCSP[9]†	88	1818	Community	General practitioners	47.8 (first ever stroke) 64.1 (TIA)
SEPIVAC[10]†	91	379	Community	General practitioners Hospital physicians	1.1
Perth[12]	93	883	Community	Physicians & nursing home supervisors	24.9
Belluno[15]	95	858	Community	Physicians & some neurologists	2
Inherred[13]	97	1169	Community	Multiple sources	10.5
Erlangen [16]	98	574	Community	General Practitioners	1.7
Arcadia[14]	99	607	Community	General practitioners	6
Zweifler[46]	98	71	Community	Paramedics	6
Kothari[47]	95	86	Community	Paramedics	28
Wester[17]	99	834	Community	Emergency room nurse	36.9
Zweifler[18]	97	100	2 different hospitals	Emergency room personnel	13
Libman[48]	95	411	Emergency department	Emergency Room personnel	19
Bratina[19]	95	112	8 different hospitals	Emergency physicians	0-19
Kothari[20]	95	446	Emergency department	Emergency physicians*	4.3
Horn[49]	97	229	Community	General practitioners	3
Martin[50]	97	565	Neurovascular clinic	General practitioners	27 (stroke) 40 (TIA)
Ferro[21]	98	174	Neurovascular clinic & emergency department	General practitioners & emergency physicians**	9

†Patients in both studies were seen as soon as possible, often prior to scanning by a stroke physician or neurologist, and excluded if thought not to have had a stroke.
*Results of CT available
**Results of CT available in 87%

Table 2. Conditions presenting with stroke like symptoms and the ranges of their relative frequency in the stroke populations identified

Final diagnosis	Proportion of total stroke population (%)	Study reference
Primary brain tumour	0.3-2.9	9;10;12;14;16;17;21;35;46;48;51
Seizure	0.3-8.5	12;17;18;20;21;35;46-48;50;51
Toxic-metabolic state	0.2-3.9	12;17;18;20;21;46-48;51
Subdural haemorrhage	0.3-1.9	9;10;12;14;16;17;21;48
Systemic infection	0.5-9.3	21;35;47;48;52
Cerebral infection	0.2-1.7	12;14;16;20;48;51
Migraine	0.4-3.0	12;14;20;35;46;50;51
Vertigo/vestibular	0.2-4.0	12;20;21;35;48;50;51
Syncope	0.2-8.5	12;17;18;20;21;47
Psychogenic	0.2-2.7	12;18;20;21;48;50;53
Peripheral neuropathy	0.5-9.3	14;18;20;21;47;51
Cerebral metastases	0.3-1.2	9;10;21;47
Transient global amnesia	0.1-1.2	12;47;48
Cardiac	0.6-2.3	35;47;48
Old stroke, nil new	1.0-1.5	17;18
Hypertensive encephalopathy	0.2-1.0	18;48
Dementia	0.5-0.8	14;48
Multiple sclerosis	0.2-1.7	14;16;20;48;50
Total non-stroke	1 – 37	

Table 3. Included stroke incidence studies

Study	Date of publication	Number of patients with stroke	Proportion undergoing scanning/post-mortem (%)
Tilberg, Holland[54]	1980	152	52
Hisayama, Japan[28]	1981	203	0
Shibata, Japan[26]	1981	415	0
Beijing, China[29]	1983	130	0
Benghazi, Libya[24]	1986	329	80
Moscow, Russia[27]	1988	1538	0
Oxford, UK[25]	1990	675	89
Akita, Japan[30]	1990	109	60
Umbria, Italy[10]	1991	375	69
Dijon, France[34]	1991	984	89
Valle D'Aosta, Italy[31]	1992	254	82
Fredricksberg, Denmark[55]	1992	262	74
FINMONICA[56]	1992	3574	30
Malmo, Sweden[33]	1992	524	51
Perth, Australia[12]	1993	492	86
Warsaw, Poland[22]	1994	462	68
Brisbane, Australia[57]	1995	2056	31
Belluno, Italy[15]	1995	474	90
Rochester, USA[23]	1996	496	90
L'Aquila, Italy[32]	1997	819	89
Tartu, Estonia[58]	1997	829	32
Innherred, Norway[35]	1997	432	88
Erlangen, Germany[16]	1998	354	96
London, UK[36]	1999	612	88
Arcadia, Greece[14]	1999	555	82

Table 4. Reasons mentioned for not scanning in community studies

Study	Proportion undergoing scanning/post-mortem (%)	Date	Reasons
Oxford	89	1988	Rapidity of death, too ill to transfer, refusal, 65% of those not scanned > 75 years
Malmo	52	1992	'Mean age of those examined by CT less than those not'
Perth	86	1993	Rapidity of death, too ill, too frail, refusal, 81% of those not scanned > 75 years
Brisbane	31	1995	'coma, lack of facility, too sick, age of the patient, attitude of the physicians'
L'Aquila	89	1997	Very early death, refusal, exclusive home care of very old patients, equipment breakdown
Tartu	32	1997	'Of the 24% with no subtype (i.e. no scan), 76% treated at home'
Erlangen	96	1998	Of those treated at home, only 37.5% scanned
London	88	1999	Community patients, died within 2 days
Arcadia	82	1999	Died early, very old, only home care, refusal, equipment breakdown

1. Von Arbin, M., Brittion, M., De Faire, U., Helmers, C., Miah, K., and Murray, V. Accuracy of bedside diagnosis in stroke. Stroke 12, 288-293. 1981.

2. Allen CM. Clinical diagnosis of the acute stroke syndrome. Q J Med 1983;52:515-23.

3. Poungvarin N, Viriyavejakul A, Komontri C. Siriraj stroke score and validation study to distinguish supratentorial intracerebral haemorrhage from infarction. BMJ 1991;302:1565-7.

4. Weir CJ, Murray GD, Adams FG, Muir KW, Grosset DG, Lees KR. Poor accuracy of stroke scoring systems for differential clinical diagnosis of intracranial haemorrhage and infarction. Lancet 1994;344:999-1002.

5. Hawkins GC, Bonita R, Broad JB, Anderson NE. Inadequacy of clinical scoring systems to differentiate stroke subtypes in population-based studies. Stroke 1995;26:1338-42.

6. Rowe CC, Donnan GA, Bladin PF. Intracerebral haemorrhage: incidence and use of computed tomography. BMJ 1988;297:1177-8.

7. Sudlow CLM,.Warlow CP. Comparable studies of the incidence of stroke and its pathological types. Results from an international collaboration. Stroke 1997;28:491-9.

8. Bogousslavsky J, Regli F, Uske A, Maeder P. Early spontaneous hematoma in cerebral infarct: is primary cerebral hemorrhage overdiagnosed? Neurology 1991;41:837-40.

9. Bamford J, Sandercock P, Dennis M, Warlow C, Jones L, McPherson K. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-86. 1. Methodology, demography and incident cases of first-ever stroke. J Neurol Neurosurg Psychiatr 1988;51:1373-80.

10. Ricci S, Celani MG, La Rosa F, Vitali R, Duca E, Ferraguzzi R. SEPIVAC: a community-based study of stroke incidence in Umbria, Italy. J Neurol Neurosurg Psychiatr 1991;54:695-8.

11. Cochrane Stroke Group search strategy for specialised register. Oxford: Update software, 2000.

12. Anderson CS, Jamrozik K, Burvill PW, Chakera TMH, Johnson GA, Stewart-Wynne EG. Ascertaining the true incidence of stroke: experience from the Perth Community Stroke Study, 1989-1990. Med J Aus 1993;158:80-4.

13. Ellekjaer H, Holmen J, Indredavik B, Terent A. Epidemiology of stroke in Innherred, Norway, 1994 to 1996. Incidence and 30-day case-fatality rate. Stroke 1997;28:2180-4.

14. Vemmos KN, Bots ML, Tsibouris PK, Zis VP, Grobbee DE, Stranjalis GS et al. Stroke incidence and case fatality in southern Greece: The Arcadia stroke registry. Stroke 1999;30:363-70.

15. Lauria G, Gentile M, Fassetta G, Casetta I, Agnoli F, Andreotta G et al. Incidence and prognosis of stroke in the Belluno province, Italy. First-year results of a community-based study. Stroke 1995;26:1787-93.

16. Kolominsky-Rabas PL, Sarti C, Heuschmann PU, Graf C, Siemonsen S, Neundoerfer B et al. A prospective community-based study of stroke in Germany-the Erlangen Stroke Project (ESPro): incidence and case fatality at 1, 3, and 12 months. Stroke 1998;29:2501-6.

17. Wester P, Radberg J, Lundgren B, Peltonen M. Factors associated with delayed admission to hospital and in-hospital delays in acute stroke and TIA. A prospective, multicenter study. Stroke 1999;30:40-8.

18. Zweifler RM, Drinkard R, Cunningham S, Brody ML, Rothrock JF. Implementation of a stroke code system in Mobile, Alabama. Diagnostic and therapeutic yield. Stroke 1997;28:981-3.

19. Bratina P, Greenberg L, Pasteur W, Grotta JC. Current emergency department management of stroke in Houston, Texas. Stroke 1995;26:409-14.

20. Kothari RU, Brott T, Broderick JP, Hamilton CA. Emergency physicians. Accuracy in the diagnosis of stroke. Stroke 1995;26:2238-41.

21. Ferro JM, Pinto AN, Falcao I, Rodrigues G, Ferreira J, Falcao F et al. Diagnosis of stroke by the nonneurologist. A validation study. Stroke 1998;29:1106-9.

22. Czlonkowska A, Ryglewicz D, Weissbein T, Baranska-Gieruszczak M, Hier DB. A prospective community-based study of stroke in Warsaw, Poland. Stroke 1994;25:547-51.

23. Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence and survival. Secular trends in Rochester, Minnesota through 1989. Stroke 1996;27:373-80.

24. Ashok PP, Radhakrishnan K, Sridharan R, El-Mangoush M. Incidence and pattern of cerebrovascular disease in Benghazi, Libya. J Neurol Neurosurg Psychiatr 1986;49:519-23.

25. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project - 1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. J Neurol Neurosurg Psychiatr 1990;53:16-22.

26. Tanaka H, Ueda Y, Date C, Baba T, Yamashita H, Hayashi M. Incidence of stroke in Shibata, Japan: 1976-1978. Stroke 1981;12:460-6.

27. Scmidt VE, Smirnov VE, Ryabova VS. Results of the seven-year prospective study of stroke patients. Stroke 1988;19:942-9.

28. Ueda K, Omae T, Hirota Y, Takeshita M, Katsuki S, Tanaka M. Decreasing trend in incidence and mortality from stroke in Hisayama residents, Japan. Stroke 1981;12:154-60.

29. Wang CC, Cheng XM, Li SZ, Liana Bolis C, Schoenberg B. Epidemiology of cerebrovascular disease in an urban community of Beijing, People's Republic of China. Neuroepidemiology 1983;2:121-34.

30. Kojima S, Omura T, Wakamatsu W, Kishi M, Yamazaki T, Iida M. Prognosis and disability of stroke patients after 5 years in Akita, Japan. Stroke 1990;21:72-7.

31. D'Alessandro G, Di Giovanni M, Roveyaz L, Iannizzi L, Compagnoni MP, Blanc S. Incidence and prognosis of stroke in the Valle D'aosta, Italy. First-year results of a community-based study. Stroke 1992;23:1712-5.

32. Carolei A, Marini C, Di Napoli M, Di Gianfilippo G, Santalucia P, Baldassarre M et al. High stroke incidence in the prospective community-based L'Aquila registry (1994-1998). First year's results. Stroke 1997;28:2500-6.

33. Jerntorp P,Berglund G. Stroke registry in Malmo, Sweden. Stroke 1992;23:357-61.

34. Giroud M, Gras P, Chadan N, Beuriat P, Milan C, Arveux P et al. Cerebral haemorrhage in a French prospective population study. Journal of Neurology, Neurosurgery & Psychiatry 1991;54:595-8.

35. Ellekjaer H, Holmen J, Indredavik B, Terent A. Epidemiology of stroke in Innherred, Norway, 1994 to 1996. Incidence and 30-day case-fatality rate. Stroke 1997;28:2180-4.

36. Stewart JA, Dundas R, Howard RS, Rudd AG, Wolfe CDW. Ethnic differences in incidence of stroke: prospective study with stroke register. BMJ 1999;318:967-71.

37. Gunatilake SB. Rapid resolution of symptoms and signs of intracerebral haemorrhage: Case reports. BMJ 1998;316:1495-6.

38. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Intracerebral hemorrhage versus infarction: stroke severity, risk factors, and prognosis. Ann Neurol 1995;38:45-50.

39. Kase CS, Caplan LR. Intracerebral haemorrhage. In Newton MA, ed. Butterworth-Heinemann, 1994.

40. Kwa VIH, Franke CL, Verbeeten Jr B, Stam J. Silent intracerebral microhaemorrhages in patients with ischaemic stroke. Ann Neurol 1998;44:372-7.

41. Greenberg SM, Finklestein SP, Schaefer PW. Petechial hemorrhages accompanying lobar hemorrhage: detection by gradient-echo MRI. Neurology 1996;46:1751-4.

42. Jamrozik K, Broadhurst RJ, Lai N, Hankey GJ, Burvill PW, Anderson CS. Trends in the incidence, severity, and short-term outcome of stroke in perth, Western Australia. Stroke 1999;30:2105-11.

43. Ueda K, Kiyohara Y, Fujishima M. Epidemiology: stroke risk factors in general population - the Hisayama study. J Stroke Cerebrovasc Dis 2000;9:27-8.

44. Hamad I, Ayman H, Sokrab S, Momani S, Mesraoua B, Ahmed AR. Incidence of stroke in Qatar. J Stroke Cerebrovasc Dis 2000;9:83-4.

45. Johansson B, Norrving B, Lindgren A. Increased stroke incidence in Lund-Orup, Sweden, between 1983 to 1985 and 1993 to 1995. Stroke 2000;31:481-6.

46. Zweifler RM, York D, Tha Tha U, Mendizabal JE, Rothrock JF. Accuracy of paramedic diagnosis of stroke. J Stroke Cerebrovasc Dis 1998;7:446-8.

47. Kothari R, Barsan W, Brott T, Broderick J, Ashbrock S. Frequency and accuracy of prehospital diagnosis of acute stroke. Stroke 1995;26:937-41.

48. Libman RB, Wirkowski E, Alvir J, Rao TH. Conditions that mimic stroke in the emergency department. Implications for acute stroke trials. Archives of Neurology 1995;52:1119-22.

49. Horn J, Limburg M, Vermeulen M. Diagnostic accuracy of stroke by family physicians. Neurology 1997;48 (suppl):A405.

50. Martin PJ, Young G, Enevoldson TP, Humphrey PR. Overdiagnosis of TIA and minor stroke: experience at a regional neurovascular clinic. QJM 1997;90:759-63.

51. Smucker WD, Disabato JA, Krishen AE. Systematic approach to diagnosis and initial management of stroke. American Family Physician 1995;52:225-34.

52. Gillard JH, Barker PB, van Zijl PCM, Bryan N, Oppenheimer SM. Proton MR spectroscopy in acute middle cerebral artery stroke. Am J Neuroradiol 1996;17:873-86.

53. Henneman PL,.Lewis RJ. Is admission medically justified for all patients with acute stroke or transient ischemic attack? [see comments]. Annals of Emergency Medicine 1995;25:458-63.

54. Herman B, Leyten ACM, Van Luijk JH, Frenken CWGM, Op de Coul AAW, Schulte BPM. Epidemiology of stroke in Tilburg, The Netherlands.2. Incidence, initial clinical picture and medical care and three-week case fatality. Stroke 1982;13:629-34.

55. Jorgensen HS, Plesner A, Hubbe P, Larsen K. Marked increase of stroke incidence in men between 1972 and 1990 in Frederiksberg, Denmark. Stroke 1992;23:1701-4.

56. Tuomilehto J, Sarti C, Narva EV, Salmi K, Sivenius J, Kaarsalo E et al. The FINMONICA stroke register: Community-based stroke registration and analysis of stroke incidence in Finland, 1983- 1985. American Journal of Epidemiology 1992;135:1259-70.

57. Shah S,.Cooper B. The epidemiology of stroke and transient ischaemia in Brisbane, Australia. Italian Journal of Neurological Sciences 1995;16:603-12.

58. Korv J, Roose M, Kaasik A-E. Stroke registry of Tartu, Estonia, from 1991 through 1993. Cerebrovasc Dis 1997;7:154-62.

3 The Importance Of Diagnosis Of Intracranial Haemorrhage In Patients Being Considered For Antithrombotic Treatment

3.1 Introduction

The dilemma of commencing antithrombotic treatment following intracranial haemorrhage

Intracranial haemorrhage, either intracerebral or subarachnoid, is usually considered an absolute contraindication to the use of antihaemostatic agents such as antiplatelet drugs or anticoagulants. However, in clinical practice, there are many occasions when it is appropriate to consider using these agents in patients with definite (or possible) intracranial haemorrhage.

In patients with definite recent primary intracerebral haemorrhage (PICH), or previous haemorrhage demonstrated with MRI, there may be an existing indication for continuing antiplatelet or anticoagulant treatment such as ischaemic heart disease or peripheral vascular disease, or a prosthetic heart valve. Or, a new indication for anticoagulation may arise such as the development of a deep vein thrombosis, pulmonary or peripheral embolus.

In patients with haemorrhagic transformation, there may be similar indications as above, as well as the need to consider secondary prevention of stroke with antithrombotic drugs if the patient is in sinus rhythm, or anticoagulants if in atrial fibrillation.

In patients with a recent stroke of unknown pathology, due to scanning not yet being available[1,2], there may be pressure to commence aspirin treatment as soon as possible if the clinical features suggest that the stroke was unlikely to be haemorrhagic, even if intracerebral haemorrhage has not been ruled out. This follows the results of the International Stroke Trial and the Chinese Acute Stroke Trial which demonstrated the benefit of aspirin if given within 48 hours of stroke onset[3].

A systematic review of the risks and benefits of antithrombotic drugs following intracranial haemorrhage.

Meta-analyses of primary and secondary prevention studies of ischaemic stroke have demonstrated a small but real risk of intracerebral haemorrhage following aspirin use[4,5]. It would therefore, be helpful to know the effect of antithrombotic drugs or anticoagulants on intracerebral haemorrhage in view of the need to consider their use. To make an estimate how much harm (if any) might be caused by the administration of antithrombotic drugs or anticoagulants to patients with recent intracerebral haemorrhage, I undertook a systematic review of the available studies of this subject. In view of the paucity of data available, the review was expanded to include all intracranial haemorrhage.

3.2 Methods

Search strategy

I sought to identify all reports of randomised trials (or observational studies with a concurrent comparison group), both published and unpublished, comparing antiplatelet or anticoagulant therapy with control following recent (CT or MRI confirmed) intracranial haemorrhage. The electronic databases MEDLINE and EMBASE were screened from January 1980 to April 2001. I also searched the Cochrane Controlled Trials Register, consulted reference lists in all articles found and cross-checked for further references. I used the extended electronic search strategy for stroke (appendix III) combined with medical subject headings: 'anticoagulant', 'anticoagulant agent', 'aspirin', 'acetyl salicylic acid', and text words 'aspirin' and acetyl salicylic acid. I deliberately kept the search broad so as to avoid missing any relevant studies in this obscure area. I searched no further back than 1980 because of the lack of readily available CT scanning before this time.

Inclusion criteria

From the papers identified by the search, I included any randomised, quasi randomised, or controlled clinical studies that described the use of antiplatelet drugs or

anticoagulants following intracranial haemorrhage, due to subarachnoid or acute intraparenchymal cerebral haemorrhage (which could be either primary intracerebral haemorrhage (PICH) or haemorrhagic transformation of an infarct, i.e. any form of bleeding inside the cranial cavity). Single case reports and studies with no concurrent comparison group were excluded.

Data extraction

From included studies, myself and another reviewer independently and blind to each other, sought and extracted data on the number and type of patients in the study, the method of treatment allocation (e.g. randomisation), the number allocated to active or control treatment, the type and dose of drug used, the duration of treatment (scheduled treatment period), the timing of latest follow up, early (during the schedule treatment period) and late (at the end of follow up) mortality, recurrent intracranial haemorrhage and recurrent ischaemic stroke, and functional outcome at the end of follow up. For recurrent intracranial haemorrhage, we sought the method by which the haemorrhage was identified, whether it was symptomatic (i.e. temporally associated with a worsening of neurological status) or not and the time when it occurred (i.e. within the scheduled treatment period or by the end of follow-up). Any disagreements regarding data extraction were resolved by discussion.

Additional individual patient data

Having identified that there were very few relevant studies in the literature, it was apparent that the majority of data would therefore come from the two largest acute stroke trials; the International Stroke Trial (IST, n = 19435)[6] and Chinese Acute Stroke Trial (CAST, n = 21106)[7], both of which investigated the use of antithrombotic therapy in acute stroke. I had access to the data from these trials, both of which investigated the use of antithrombotic therapy within 48 hours of acute stroke. About 17% were randomised within six hours, and 33% within 12 hours. In these trials, patients could be randomised before CT scanning if the clinical suspicion of acute intracerebral haemorrhage was low and the CT scan was likely to be delayed. As a result, a small proportion of patients who were randomised without a CT scan and started the trial

treatment, were found to have had an acute intracerebral haemorrhage when scanned subsequently (n = 773). These patients were described as having 'haemorrhagic stroke' on the study's data forms. Prior to analysing the individual patient data, I also reviewed the individual original IST record forms to extract any additional information on the nature or timing of the intracranial haemorrhage and duration of trial treatment (i.e. whether it was discontinued early or not).

Analyses

All trials were analysed together first of all (i.e. in patients with any intracranial haemorrhage), and then I looked specifically at just intraparenchymal cerebral haemorrhage and examined the effect of aspirin, heparin and other antiplatelet agents at various early and late outcomes. Individual patient data were used when available. RevMan software (as used in the Cochrane Database of Systematic Reviews) was used to provide an estimate of treatment effect, using the Peto odds ratio (OR), fixed effects method and 95% confidence limits. In view of the paucity of data, it did not seem appropriate to undertake sensitivity analyses or attempt to give the studies a quality score. Rather I focussed on ensuring that randomised studies genuinely used random treatment allocation, on details of follow-up and outcome, to ensure a basic minimum standard.

3.3 Results

Included studies

The search strategy identified 2779 papers on antithrombotic or anticoagulant treatment or intracranial haemorrhage, but of these, only nine described a trial of antithrombotic or anticoagulant treatment in patients with intracranial haemorrhage, and two described retrospective observational studies. Of the nine trials (2043 patients) of antiplatelet drugs (1997 patients) or anticoagulants (645 patients) given after acute intracranial haemorrhage that were identified, including the IST and CAST[6-14] (tables 1 and 2), eight were randomised trials[6-11,13,14], and one was a double-blind comparative study that gave no information on whether treatment allocation was randomised or not[12]. However, on

balance, it was decided to include it. An additional publication that added an extra group of patients to a trial already included in the review[11] was excluded[15].

Characteristics of the included trials

The intracranial haemorrhage was due to subarachnoid haemorrhage in six trials (1224 patients)[8-10,12-14], a mixture of acute intraparenchymal cerebral haemorrhage and haemorrhagic transformation of cerebral infarction in two trials (773 patients)[6,7], and proven primary intracerebral haemorrhage in one (46 patients)[12]. In two of the subarachnoid haemorrhage trials, the antiplatelet trial drugs were given *after* the aneurysms had been surgically clipped to prevent rebleeding[13,14]; in one the antiplatelet trial drugs were definitely started *before* any clipping of the aneurysm[10]; and in three trials there was no indication of whether the aneurysm had been securely treated or not prior to starting the antiplatelet trial drugs[8,9,12].

The duration of the scheduled treatment period ranged from eight days[13] to three months[10], and three studies did not clearly specify the duration of treatment[8,9,11] The length of follow-up ranged from one[7,13] to six[6,9] months, and one study did not specify length of follow-up[11].

The primary outcome was (Table 1, 2):
death in four studies: within the scheduled treatment period in two studies[6,7], within the follow-up period of six months in one study[9]; and the time period was not specified in one study[11]; "neurological disability" measured by Glasgow Outcome Score in two studies[10,13]; the Japanese Coma Scale in one study[12], and was unspecified in two studies[8,9]; functional outcome (i.e. Rankin or simplified equivalent) in three studies[6,7,14]; and pulmonary embolus and deep vein thrombosis in one study[11].

Three studies (466 patients – two in SAH and one in intraparenchymal cerebral haemorrhage) systematically scanned patients at repeated time intervals[8,11,12], but did not define whether any recurrent intracranial haemorrhage that occurred had been identified by routine scanning or because of clinical deterioration. Only two studies (773 patients) documented that recurrent intracranial haemorrhage occurred during the scheduled

treatment period[6,7]. The remaining studies did not specify whether recurrent intracranial haemorrhage occurred within the scheduled treatment period or by the end of follow-up. It was therefore assumed that any recurrent intracranial haemorrhages reported had simply occurred at some point within the period of follow-up.

Additional individual patient data

The IST and CAST randomised 40541 patients, of which 7758 (19%) were first CT scanned after randomisation. Of these patients, 773 (10%) were found to have an acute intracerebral haemorrhage when scanned, of whom 398 patients had been allocated to aspirin (375 to control), and 310 to heparin (289 to control). On review of the individual IST forms, 58% of the intracerebral haemorrhages were said to be primary intracerebral haemorrhage and 42% were said to be haemorrhage transformation of an infarct. The trial treatment was stopped after the post-randomisation CT scan in 65% of these patients who therefore only received a few doses of the trial treatment. However, all 773 patients were included in the present analysis. We were not able to compare outcomes in the patients who received only a few doses of antithrombotic treatment with those who received more antithrombotic treatment because the sample size was too small and confidence intervals already too wide to provide reliable conclusions (see below). Nor unfortunately were we able to examine the effect of time to randomisation on treatment for the same reasons.

Effect of antiplatelet treatment on outcome after acute intracranial haemorrhage (i.e. subarachnoid or intraparenchymal cerebral haemorrhage) and after intraparenchymal cerebral haemorrhage alone.

All recorded deaths

In patients with any acute intracranial haemorrhage (1997 patients), the odds ratio for death among patients allocated to antiplatelet treatment compared with control was 0.85 (95% CI 0.63 to 1.15) (figure 1).

In patients with just intraparenchymal cerebral haemorrhage (773 patients), the OR for death among patients allocated to antiplatelet treatment compared with control was 0.96 (95% CI 0.62 to 1.50) (Figure 1).

Recurrent intracranial haemorrhage

In patients with any acute intracranial haemorrhage, the odds ratio for recurrent intracranial haemorrhage among patients allocated antiplatelet treatment compared with control was 1.00 (95% CI 0.73 to 1.37) (figure 2).

In patients with just intraparenchymal cerebral haemorrhage (773 patients) the odds ratio for recurrent intracranial haemorrhage among patients allocated to antiplatelet treatment compared with control was 1.02 (95% CI, 0.58, 1.8).

Functional outcome

Data on functional outcome at six months were only available from the IST[6] (599 patients). Although data on functional outcome were collected in CAST[7] this was only at one month and therefore was regarded as too short term. The odds ratio for being dead or dependent among patients with intracranial parenchymal haemorrhage allocated to antiplatelet treatment compared with control was 0.68 (95% CI 0.46 to 1.02). However, 65% of patients allocated to aspirin treatment received no more than a few doses of aspirin, so this does not reflect the effect of full dose aspirin. In any case, 42% were considered to be haemorrhagic transformation of an infarct in which case aspirin may have had some beneficial effect.

Effect of anticoagulant treatment on outcome after acute intraparenchymal cerebral haemorrhage

There were no data on the use of anticoagulants after SAH.

All recorded deaths

Among patients with any acute intraparenchymal cerebral haemorrhage (645 patients) comparing these allocated to heparin with control, the odds ratio for death in the scheduled treatment period was 0.96 (95% CI 0.38 to 2.40) (figure 3). For the 599/645 patients from the IST included in this analysis, the heparin was stopped after a few doses in 65% on discovering the intracranial haemorrhage.

Recurrent intracranial haemorrhage

Among patients with acute intraparenchymal cerebral haemorrhage, the odds ratio for recurrent intracranial haemorrhage among patients allocated heparin compared with control was 2.0 (95% CI 0.86 to 4.70) (figure 4).

Functional outcome

Among patients with acute intraparenchymal cerebral haemorrhage, data were available only from the IST for functional outcome at six months (n = 599)[6]. The odds ratio for being dead or dependent among patients allocated heparin compared with control was 0.97 (0.66 to 1.43).

Figure 1. Effect of antiplatelet treatment on death in patients with recent intracranial haemorrhage. Systematic review of randomised trials comparing antiplatelet agent with control in patients with recent subrachnoid haemorrhage or intracerebral haemorrhage. Expt = patients allocated antiplatelet, Ctrl = patients allocated control, n = number of patients with event, N = number of patients allocated to that treatment, Peto OR = odds ratio calculated using the Peto method, Weight = proportion of the total amount of information in the whole review attributable to this study, 95% CI (fixed) = 95% confidence intervals using a fixed effects model.

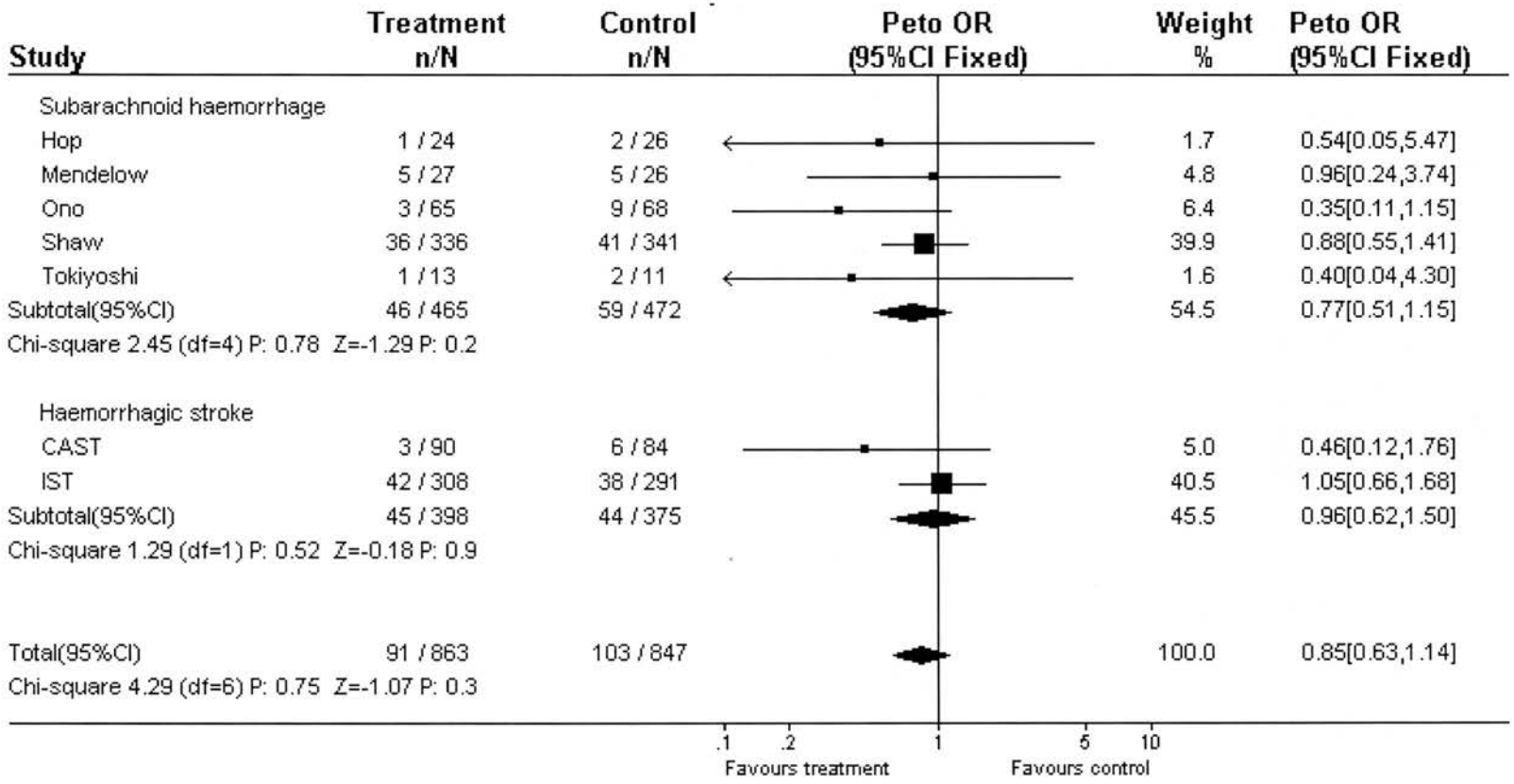


Figure 2. Effect of antiplatelet treatment on recurrent intracranial haemorrhage in patients with recent intracranial haemorrhage (same conventions as fig. 1).

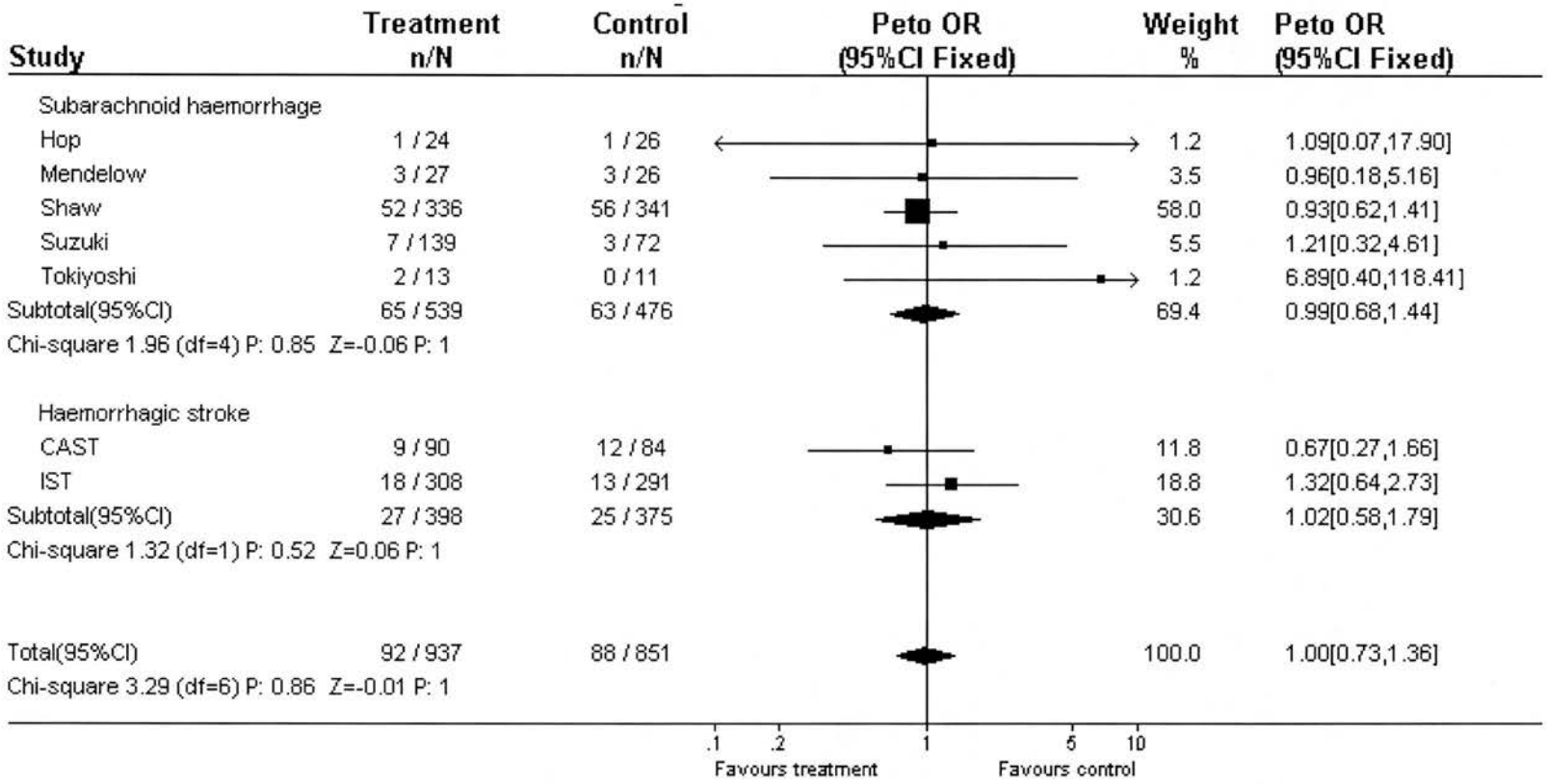


Figure 3. Effect of heparin on death in patients with recent intracranial haemorrhage. Systematic review of trials comparing heparin with control (same conventions as fig. 1).

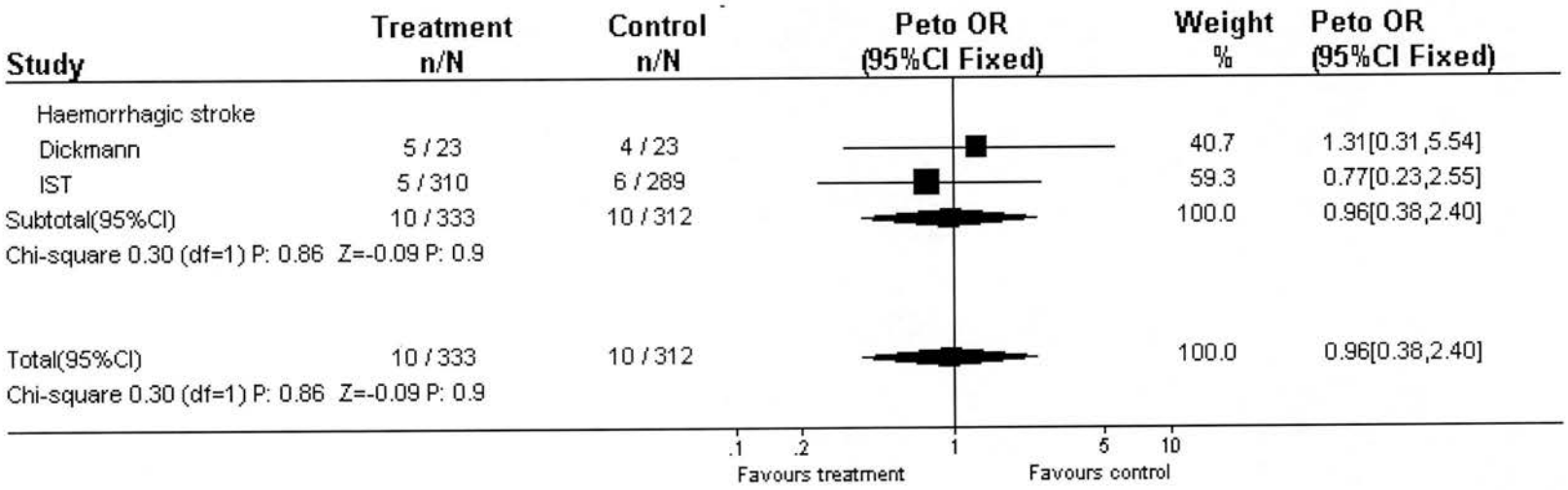
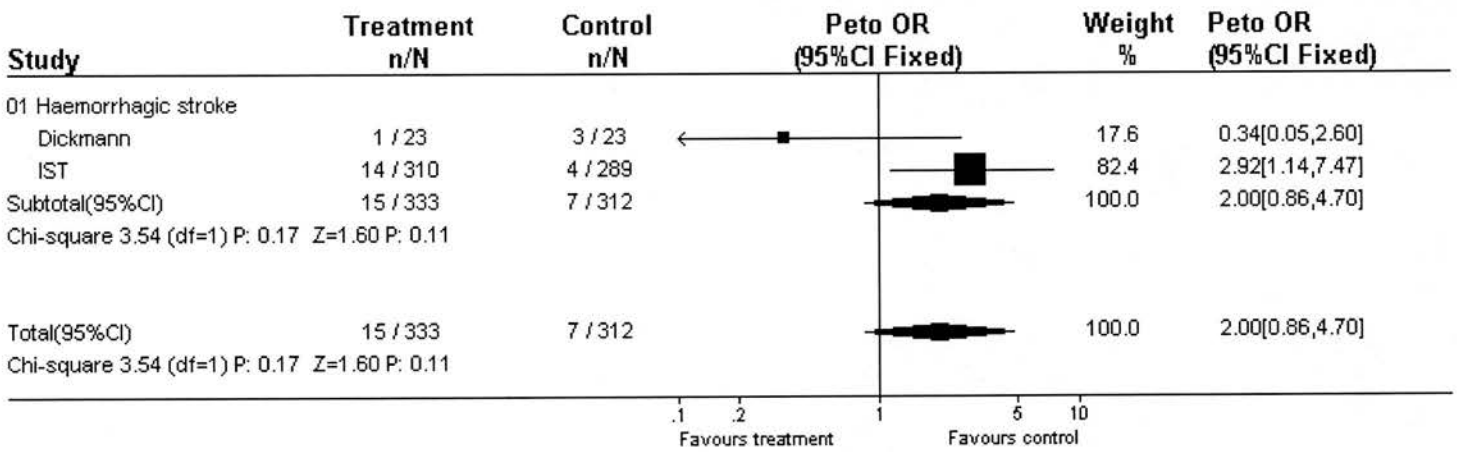


Figure 4. Effect of heparin on recurrent intracranial haemorrhage in patients with recent intracranial haemorrhage (same conventions as figure 1)



Data from observational studies

Two observational studies were also identified (table 3), both concerning patients with subarachnoid haemorrhage. One retrospectively examined the effect of heparin given during surgery if a neurological deficit occurred, or after surgery as prophylaxis, compared with patients with subarachnoid haemorrhage who were not given heparin[16]. In this study, there were less patients with recurrent haemorrhage in the group treated with heparin (9.6% versus 26.1% for controls). The study by Juvela retrospectively assessed the use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) prior to and after subarachnoid haemorrhage[17]. Since NSAID's primary mode of action is not antiplatelet, we restricted our analyses to the aspirin and no aspirin groups. There were fewer deaths and fewer recurrent haemorrhages among patients receiving aspirin than among controls (Table 3).

3.4 Discussion

What are the limitations of these data?

To the best of my knowledge, this review summarises the totality of the evidence from randomised trials or studies with a comparative control group on antithrombotic or anticoagulant drugs after acute intracranial haemorrhage.

There are many limitations to these scant data. Sixty percent of the data on antiplatelet agents came from patients with subarachnoid haemorrhage rather than intracerebral (i.e. brain parenchymal) haemorrhage, and at least some (it is not clear from the papers how many) of those patients had received definitive treatment of their aneurysm to prevent rebleeding before starting the antiplatelet trial treatment. The subarachnoid haemorrhage data may be of limited relevance to patients with primary intraparenchymal cerebral haemorrhage. For the data on patients with intraparenchymal cerebral haemorrhage, the extent to which conclusions may be drawn on the *safety* of antithrombotic treatment are limited by the fact that in the majority (65%), the aspirin or heparin was discontinued after only a few doses upon discovery that the stroke was haemorrhagic. Therefore the data *do not* describe a situation where full dose aspirin (or

heparin) was given to patients with intraparenchymal cerebral haemorrhage either for two weeks in the acute stage, or indefinitely as might happen in error if a stroke was assumed to be ischaemic on clinical grounds without exclusion of haemorrhage by scanning. Almost all (94%) of the data on the effects of heparin in acute intraparenchymal cerebral haemorrhage come from the IST – these were a highly selected group of patients in the sense that it was only possible to randomise patients into the IST prior to CT scanning if the local investigator felt that intraparenchymal cerebral haemorrhage was unlikely to be the cause of stroke on clinical grounds. Out of 7758 patients randomised prior to CT, only 773 (10%) turned out to have intraparenchymal cerebral haemorrhage on CT. Thus this group of patients is not likely to be representative of intracranial haemorrhage in general and conclusions must be drawn with great caution.

How does this evidence help with clinical decision-making?

Despite these problems, some inferences of clinical value can still be drawn from this information. For antiplatelet drugs, the point estimates of effect on death and recurrent intracranial haemorrhage for patients with any intracranial haemorrhage are neutral or favourable, though less so if just patients with intraparenchymal cerebral haemorrhage are examined (the group relevant to haemorrhagic stroke). The available evidence cannot rule out modest harm, but equally they are also consistent with moderate benefit. The low risk of further intracranial bleeding in patients with intracranial haemorrhage is consistent with the low intracerebral bleeding risk with these agents observed in other settings, although the fact that 65% of patients discontinued treatment after only a few doses is important. Thus, in certain situations, the use of an antiplatelet agent soon after acute intracranial haemorrhage would be justified perhaps if the patient were at particularly high risk of cardiac ischaemic events, as a result of a recent myocardial infarction or had a history of unstable angina[5]. The data do *not* allow us to answer the question about use of antithrombotic drugs in patients with a new ischaemic cerebral event who have had a known intracranial haemorrhage at some point in the more remote past, *or* about the long term effects in patients with recent intracranial haemorrhage if required for prevention or treatment of some other vascular complication.

The risks associated with heparin were only assessed for subcutaneous, not intravenous heparin, and only in patients with intraparenchymal cerebral haemorrhage. Whilst the lack of effect of heparin on deaths from all causes was reassuring, the non-significant trend to a doubling of the risk of recurrent intracranial haemorrhage with heparin is a concern. Yet, patients with intracranial haemorrhage do develop indications for the use of heparin such as symptomatic deep vein thrombosis (DVT). It would be useful to know precisely the balance of risk and benefit of giving heparin, and whether the reductions in venous thromboembolism are offset by an increase in intracranial haemorrhage. Unfortunately, the available data do not answer this question reliably.

Do these data aid scanning policy?

These data support the policy, in centres where CT resources are limited and access may be delayed, of 'start aspirin pending CT if acute intracerebral haemorrhage is unlikely on clinical grounds', and 'stop the aspirin if the patient turns out to have a haemorrhage when scanned', provided the CT scan can be obtained within a day or so of starting treatment. The value of aspirin where CT scanning is not performed until five to seven days later (or more) or not at all, is not assessed by these data. A policy of widespread use of aspirin without prior imaging – a suboptimal policy - in places where CT scanning is available is not supported by these data. In places where CT scanning is not available *at all*, widespread use of aspirin among patients with a high probability of having an ischaemic stroke (e.g. selected with a clinical scoring system such as the Siriraj score[18]) may well be reasonable, as the population benefits of aspirin may outweigh the risks. However, such a policy would require further testing and these data certainly provide no more than modest support for such an approach.

Table 1. Characteristics of randomised trials of antithrombotic agents given following subarachnoid haemorrhage primarily for the prevention of delayed ischaemic neurological deficit

Study Year	No of patients	Intervention	Methods	Scheduled treatment period	Duration of follow-up (months)	Primary outcome	Comments
Trial treatment started prior to surgical treatment of the aneurysm							
Shaw[10] 1985	677	Dipyridamole 100mg PO, or 10mg IV, OD	Randomised open trial	3 months	3	Neurological disability	Patients randomised immediately on admission, before investigations
Not certain whether aneurysms treated prior to start of trial treatment							
Mendelow[9] 1982	53	Aspirin 300mg PO BD, or placebo	Randomised placebo-controlled trial	3 days after admission until discharge	6	Death, neurological disability	All patients received tranexamic acid PO or IV
Ono[8] 1984	135	Ticlopidine 100mg PO TDS or placebo	Randomised double-blind placebo controlled trial	Not stated	3	Neurological disability	No specific data on recurrent haemorrhage although quoted 'no significant increase in haemorrhagic complications occurred'
Suzuki[12] 1989	285	OKY-046* 80mg IV BD, 400mg IV BD, or placebo	Multicentre double-blind comparative study	10-14 days	3	Neurological disability	No information on method of treatment allocation. Aspirin avoided during treatment schedule
Trial treatment started after surgical treatment to prevent aneurysm rebleeding							
Tokiyoshi[13] 1991	24	Cataclot*† 1μg/kg/min versus placebo	Randomised trial	8 – 14 days	1	Neurological disability	No information on blinding
Hop[14] 2000	50	Acetylsalicylic acid (ASA) 100mg PR versus placebo	Randomised trial	21 days	4	Functional outcome	Pilot study

OD = once daily; BD = twice daily; TDS = thrice daily; PO = by mouth
*Thromboxane synthesis inhibitor,
†Sodium (E)-3-[p-(1H-imidazol-1-ylmethyl) phenyl]-2-propenoate

Table 2. Characteristics of randomised trials of antithrombotic agents given following haemorrhagic stroke or primary intracerebral haemorrhage

Study year	Number of patients	Intervention	Methods	Scheduled treatment period	Duration of follow-up (months)	Primary outcome	Comments
Dickmann[11] 1988	46	Heparin 5000u SC TDS versus control.	randomised, open trial in patients with intracerebral haemorrhage.	not specified	not specified	death, DVT, PE, rebleeding	Heparin given from day 4, compared with control (heparin started day 10).
IST[6] 1997	599	Aspirin 300mg PO/PR, heparin (12500u BD 25000u SC), both or neither.	randomised, open trial in patients with acute stroke. blinded outcome assessment	14 days	6	death within 14 days death or dependency at 6 months	Patients could be randomised prior to CT scanning if there was a low clinical suspicion of intracerebral haemorrhage. total trial size: 19435 patients
CAST[7] 1997	174	Aspirin 160mg PO versus control.	randomised placebo-controlled trial in patients with acute stroke.	up to 4 weeks	until discharge (average 4 weeks)	deaths, death or dependency at discharge	Same CT scanning policy as IST. total trial size 21106 patients

*thromboxane synthetase inhibitor
†Sodium (E)-3-[p-(1H-imidazol-1-ylmethyl) phenyl]-2-propenoate
OD = once daily; PO = by mouth; BD = twice daily; IV = intravenous; TDS = thrice daily; PR = per return, SC = subcutaneous
DVT = deep vein thrombosis; PE = pulmonary embolus

Table 3. Non-randomised studies

Study	Number of patients	Methods	Comments
Kapp[16] 1987	161	Retrospective observational study in patients with subarachnoid haemorrhage undergoing gradual carotid ligation. 115 had heparin (2500u – 3500u, dose adjusted), 46 had no heparin	Recurrent intracranial haemorrhage: Prophylactic heparin or heparin after deficit 11/115 (9.6%). No heparin 12/46 (26%).
Juvela[17] 1995	291	Observational study on retrospective use of aspirin and NSAIDs prior to or after subarachnoid haemorrhage 62 had taken aspirin before or within 7 days of SAH**, 144 had no aspirin/NSAIDs (control)	Aspirin (n = 62) / No aspirin (n = 144) Death in study period: 18% / 23% Recurrent haemorrhage: 19% / 31%

*nonsteroidal anti-inflammatory drug
**subarachnoid haemorrhage

1. Muir KW, Weir CJ, Murray GD. Comparison of neurological scales and scoring systems for acute stroke prognosis. Stroke 1996;27:1817-20.

2. Hawkins GC, Bonita R, Broad JB, Anderson NE. Inadequacy of clinical scoring systems to differentiate stroke subtypes in population-based studies. Stroke 1995;26:1338-42.

3. Chen ZM, Sandercock P, Pan HC, Counsell C, Collins R, Liu LS et al. Indications for early aspirin use in acute ischemic stroke : A combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. Stroke 2000;31:1240-9.

4. Jiang He, Whelton PK, Vu B, Klag MJ. Aspirin and risk of haemorrhagic stroke. A meta-analysis of randomised controlled trials. JAMA 1998;280:1930-5.

5. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. British Medical Journal 308, 81-106. 1994.

6. Anonymous. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet 1997;349:1569-81.

7. Anonymous. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet 1997;349:1641-9.

8. Ono H, Mizukami M, Kitamura K, Kikuchi H. Subarachnoid haemorrhage. Agents Actions suppl 1984;15:259-72.

9. Mendelow AD, Stockdill C, Steers AJW, Hayes J, Gillingham FJ. Double-blind trial of aspirin in patients receiving tranexamic acid for subarachnoid haemorrhage. Acta Neurochirurgica 1982;62:195-202.

10. Shaw MD, Foy PM, Conway M, Pickard JD, Maloney P, Spillane JA et al. Dipyridamole and postoperative ischemic deficits in aneurysmal subarachnoid hemorrhage. J.Neurosurg. 1985;63:699-703.

11. Dickmann U, Voth E, Schicha H, Henza T, Prange H, Emrich D. Heparin therapy, deep vein thrombosis and pulmonary embolism after intracerebral haemorrhage. Klin Wochenschr 1988;66:1182-3.

12. Suzuki S, Sano K, Handa H, Asano T, Tamura A, Yonekawa Y et al. Clinical study of OKY-046, a thromboxane synthetase inhibitor, in prevention of cerebral vasospasms and delayed cerebral ischaemic symptoms after subarachnoid haemorrhage due to aneurysmal rupture: a randomized double-blind study. Neurological Research 1989;11:79-88.

13. Tokiyoshi K, Ohnishi T, Nii Y. Efficacy and toxicity of thromboxane synthetase inhibitor for cerebral vasospasm after subarachnoid haemorrhage. Surg Neurol 1991;36:112-8.

14. Hop JW, Rinkel GJ, Algra A, Berkelbach van der Sprenkel JW, van Gijn J. Randomized pilot trial of postoperative aspirin in subarachnoid hemorrhage. Neurology 2000;54:872-8.

15. Boeer A, Voth E, Henze Th, Prange HW. Early heparin therapy in patients with spontaneous intracerebral haemorrhage. J Neurol Neurosurg Psychiatr 1991;54:466-7.

16. Kapp J, Neill WR, Salter JE, Barnes TY. Systemic heparin in the early management of ruptured intracranial aneurysms: Review of 104 consecutive cases and comparison with concurrent controls. Neurosurgery 1987;20.

17. Juvela S. Aspirin and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. J Neurosurg 1995;82:945-52.

18. Poungvarin N, Viriyavejakul A, Komontri C. Siriraj stroke score and validation study to distinguish supratentorial intracerebral haemorrhage from infarction. BMJ 1991;302:1565-7.

4 The Sensitivity Of CT And MRI In The Identification Of Intracerebral Haemorrhage

4.1 Introduction

Distinguishing intracerebral haemorrhage from ischaemic stroke is important

Chapter 2 demonstrated how inaccurate stroke incidence studies may have been in their identification of the proportion of patients with intracerebral haemorrhage (ICH). Chapter 3 showed that, although data are limited, there is the potential to cause harm if antithrombotic drugs are given acutely following ICH. Aspirin may cause relatively less recurrent ICH than heparin following stroke[1] but is associated with a small but definite risk[2,3]. Therefore, it is important to distinguish ICH from ischaemic stroke prior to commencing antithrombotic therapy or giving thrombolysis.

CT or MRI, which is 'better'?

Although access to MRI in the investigation of stroke has increased, CT is still by far the most common type of brain imaging used[4,5]. It is also likely to remain so for the foreseeable future as, compared to MRI, it is more readily available and easier to perform. Haemorrhage can be easily demonstrated on CT as soon as clinical symptoms appear[6]. However, these changes remain visible for only a finite amount of time[7,8]. The issue of sensitivity of CT in the identification of ICH is less whether it can distinguish acute ICH from ischaemic stroke, but rather the length of time for which these changes remain visible and reliably differentiated from ischaemic stroke. Haemorrhage remains visible on MRI for much longer[9] and also has advantages over CT in the lack of exposure of the patient to ionising radiation, as well as the level of detail of anatomical structure it is possible to achieve. However, MRI is contraindicated for patients with pacemakers and certain metal implants, and having the patient enclosed in a tunnel can render them claustrophobic and make monitoring difficult. MRI takes longer than CT, which may be relevant when scanning a population of acutely unwell people. If MRI can only be safely and reliably used by a small proportion of a non-selected stroke

population, it can hardly be hailed as the imaging modality of choice, however impressive the results in highly selected individuals.

Why perform a systematic review of imaging studies?

As mentioned in the introduction, diagnostic tests have not often been subjected to the systematic review process. There is no existing systematic review of the use of CT or MRI scanning in stroke. From the 1970's to the early 1990's, when CT scanning for stroke was less available than today, there was perhaps less of a need for precise estimates of its accuracy. Compared with nothing (or existing investigations such as air encephalography), CT provided abundant information. However, CT is now more available, stroke is a common problem, and there are now treatments which depend upon knowing the cause of the stroke. The misuse of imaging could create a very costly burden to the Health Services. The development of MRI poses similar but possibly greater problems as increasingly sophisticated and seemingly advantageous techniques are developed. I therefore undertook a systematic review of the use of CT and MRI, either alone or in combination, in the identification of haemorrhagic stroke, not only to look for details on sensitivity, but also assess the quality of the methodology of the studies performed.

4.2 Methods

Search strategy

I performed an electronic search of the medical databases, MEDLINE from the 1966 to the present day (MEDLINE databases are broken down into time periods, and the earliest time period is 1966 to 1974, which overlaps with the inception of CT) and EMBASE from 1980 (which was as far back as it was possible to search) to the present day. To an extended search strategy for stroke (appendix III) were added specific search terms for accuracy, sensitivity and specificity, and for CT and MRI. Because patients with haemorrhagic and ischaemic stroke present with the same symptoms and were often studied together, the main search strategy was designed to identify studies of ischaemia as well as haemorrhage. Conference abstracts were also scanned, and further

studies were identified by examination of the reference lists of studies already found. Preliminary searches specifically for the accuracy of scanning in ICH revealed very limited data. Therefore, the inclusion criteria were deliberately broad, to encompass all studies of the use of CT and/or MRI in humans with ICH. Case reports were excluded.

Data extraction

The following data were extracted on:

- The size of study;
- Its primary purpose;
- Details of the patient population and stroke severity;
- Whether the study was prospective;
- Timing of scanning in relation to onset of stroke symptoms;
- In studies comparing CT and MRI, the timing of each type of scan in relation to each other;
- Whether the order of CT and MRI was random or not;
- Whether scans were read blinded to clinical details or other imaging; and any data on sensitivity available.

Data were also collected on whether patients in the study had been examined by a stroke physician or neurologist, (which was assumed to be the case if the study was from a department of neurology or neurosurgery, even if there was no reference in the text), compared to a more general population referred for imaging by clinicians with less experience of stroke presentation. Any information on clinical feasibility and acceptability of scanning (e.g. the number of patients unable to tolerate scanning, or number of inadequate images) was noted.

Data analysis

Included studies were entered into an Access database and assessed with descriptive statistics.

4.3 Results

4.3.1 CT and the identification of haemorrhage

Included studies

1047 references pertaining to the accuracy of CT alone in stroke (haemorrhagic and ischaemic) were captured, and their abstracts reviewed. Fifty-three studies (including a total of 4491 patients) that were specifically concerned with ICH identified by CT were identified (table 1). Studies in which both CT and MRI were performed at some stage were analysed separately (see 4.3.3). Studies concerning inter-observer reliability of image interpretation (some of which included ICH) will be addressed in chapter 6.

Twenty-four studies (1310 patients) described various characteristics of ICH in an anatomically specific site (clinicotopography), merely documenting the scan findings in groups of patients with similar clinical symptoms (often retrospectively identified). Nineteen studies (2138 patients) attempted to predict prognosis following ICH, using clinical or imaging parameters. Both of these groups of studies used CT uncritically as the tool to identify and characterise haemorrhage(e.g. site, size, extension), and as such provided no information on accuracy.

Studies concerning haemorrhage on CT at differing time-points

Six studies (819 patients) documented CT characteristics of haemorrhage at different time points[7,8,10-13]. Two of these (623 patients) reviewed a population with acute ICH and multiple scans within the first few days after ictus, looking for the proportion of patients with haematoma enlargement[10,11]. One study (204 patients) found that 17% of haematomas continued to expand after six hours, but that further enlargement after 24

hours was rare[10]. The other (419 patients) found 14.3% of haematomas had expanded between the first CT (within 24 hours of onset of symptoms) and second CT (within 24 hours of admission)[11]. Both used retrospectively collected data and scans were not read blinded to each other, but they highlight the important point that one scan of an acute haematoma is merely a snapshot in a dynamic process.

Two studies (160 patients) investigated residual lesions late after ICH. Initial scans were within a week of onset of stroke symptoms and follow-up scans were over two months afterwards. Between 17%[12] and 27%[13] showed no residual lesions at all. Areas of hypodensity that would be indistinguishable from ischaemic stroke were found in 37%[13] to 52%[12]. Focal calcification was found in 5%[12] to 10%[13]. Slit-like hypodense lesions were identified in 14%[12] to 25%[13] at the site of previous haemorrhage, but it is not clear whether these are only found following ICH.

Two studies (36 patients) commented on the time-course over which signs of haemorrhage could disappear. One study looking at small haemorrhages (less than 20mm, comprising 6% of their ICH population) performed follow-up scanning between six days and three months in 8/31 (26%) patients. They found that 2/8 (25%) were isodense within nine days of stroke[7]. The other study reported on five patients with ICH (maximum diameter 33mm), identified as part of a community stroke incidence study, in whom the haematomas had become isodense on repeat CT within a few weeks of the original scan. The earliest repeat CT had been performed 13 days after stroke, and it is possible that the haematomas may have become isodense earlier[8].

Studies of haemorrhagic transformation

One study (15 patients) reported a case series of patients with ischaemic stroke who had undergone neuroimaging twice within the first 24 hours, the first scan negative and the second scan positive for haemorrhage[14]. They raised the issue that early haemorrhagic transformation may present as primary intracerebral haemorrhage if patients are not scanned very early. Unfortunately, they did not document the proportion of patients in their population that this group represented.

Increasing use of CT and the incidence of ICH

Two studies not based on case series were also identified that investigated the incidence and outcome of cases of ICH in relation to the use of CT. One study found that the rising incidence of ICH in their institution paralleled their use of CT[15], and both found that case fatality of ICH dropped with increasing use of CT[15,16], i.e. smaller, less deadly ICH was being identified with increased frequency as more patients were being scanned with CT.

General methodological details

Methodological detail in the majority of these studies was poor; although in 36 studies (71% of total identified) patients were assessed by a stroke physician or neurologist, information on stroke type and severity were very limited, as was timing of scanning in relation to onset of stroke symptoms. Only two studies blinded scan readers to clinical history[17] or other imaging[14]. Only six studies (12%, 656 patients) documented that cases were collected prospectively or consecutively[7,17-21]; the majority of studies used retrospectively collected data. There were no other standards used (e.g. post-mortem) against which CT could be judged, although admittedly this would have introduced a bias towards the more severe strokes. There were no papers identified on CT alone and ICH after 1998.

Summary of studies of CT and ICH

Acute ICH on CT is very characteristic and immediately visible but the only data on the length of time these features last are anecdotal. No studies were found where the primary purpose was to establish the sensitivity of CT in the identification of haemorrhage at specific time points after stroke. There may be features characteristic of previous haemorrhage on CT but there are no data on how specific they are, or how reliably they can be interpreted. Increased use of CT has led to the realisation that ICH can cause mild stroke or even transient ischaemic attacks[22].

4.3.2 *MRI and the identification of haemorrhage*

Included studies

2098 references were captured concerning MRI and stroke, either alone or in combination with CT, and their abstracts were reviewed. Twenty-two studies (1512 patients) concerning MRI and ICH were identified (table 2). Eight studies (235 patients) concentrated on MRI alone in ICH. Four were technical studies[23-26] investigating specific MRI sequences and their use in ICH, two of which (82 patients) demonstrated the superiority of gradient echo (GRE) technique over other MRI sequences in the identification of ICH [23,26]. Five (47 patients) were descriptive case studies, documenting the clinical characteristics and signs seen on imaging (clinicotopography) of haemorrhage on MRI[27-31]. Six studies (427 patients), although including a small number of patients with haemorrhage, were primarily concerned with comparing CT and MRI in ischaemic stroke, and thus little information could be drawn from these[32-37]. None of these studies documented numerical data on the sensitivity of MRI for identification of ICH. In 14 studies (1239 patients), CT was also performed at some stage.

4.3.3 *Studies that directly compared CT and MRI*

In only two studies (165 patients) were MRI and CT scanning performed at similar times enabling some comparison of sensitivity to be made (table 3). One (published in 2000) investigated the incidence of haemorrhagic transformation in cerebral infarction[38], and the other (published in 1990) the sensitivity of both modes of scanning in intracranial haematoma[39]. Imaging was performed in both studies 'acutely' (less than two days), 'subacutely' (between two and ten days) and in the 'chronic' phase (over 10 days). In only one of the studies were images read blinded (to clinical details but not to other imaging[38]). These studies suggested that in the acute phase, CT was more sensitive in identifying haemorrhage and MRI was better in the chronic phase. One study used specific blood-sensitive sequences (gradient echo)[39]. Neither study mentioned the order in which scans were performed, or whether they were performed on the same day.

One small study (nine patients) that retrospectively compared CT and MRI in patients with hyperacute ICH[40] described how MRI demonstrated haemorrhage in all cases. The main conclusion of the study was that acute haemorrhage could be detected on MRI as easily as CT, which is generally held not to be the case. The methodological weakness of the study (patients were retrospectively identified from an already highly selected cohort, and images were read unblinded by stroke physicians highly trained in MRI interpretation) make their conclusion impossible to extrapolate to a more general stroke population.

MRI and asymptomatic haemorrhage

Five studies (653 patients) used MRI to investigate the incidence of previous (asymptomatic) haemorrhage, as demonstrated by the presence of paramagnetic breakdown products of haemoglobin[41-45] (table 4). The study populations varied in age and clinical history, and included patients with a history of ICH, ischaemic stroke and also some with no history of cerebrovascular disease. Signs indicating asymptomatic haemorrhage were identified in up to 66% and 36% respectively. In patients with a history of ICH, MRI scans were performed 3 days to two years after the event.

General methodological details

14/22 studies (1119 patients) included patients that had been assessed by a stroke physician or neurologist[24,27-29,32-34,36-38,41,42,44,46]. Only eight (43%) studies (755 patients) reported any details on the case-mix of patients[28;29;32-34;41;42;44]. Eight (38%) studies (865 patients) gathered data prospectively[32-34,37,38,41,43,44]. Only five (23%) studies (643 patients) read scans either blinded to other imaging[33] or clinical history [32,34], or both[38,44]. Only one (5%) study comparing CT to MRI attempted to randomise the order in which imaging was performed[34].

Summary of MRI studies

The only studies that directly compared CT to MRI in the detection of ICH were small (138 patients in total), and had substantial flaws in their study method, making their conclusions difficult to generalise to an unselected stroke population. There were no studies investigating the length of time for which signs of haemorrhage persist on MRI after stroke. There were no studies concentrating on the feasibility of MRI in an unselected stroke population, or the acceptability of MRI for patients. No study gave details of the absolute proportion of patients presenting to their hospital with stroke symptoms who weren't scanned because MRI was unavailable, or in whom MRI was deemed unsafe, or contraindicated.

4.4 Discussion

CT identifies ICH but it is not possible to derive its sensitivity

Published studies demonstrate that ICH on CT appears acutely as an area of obvious hyperdensity, but the duration of its appearance is time-dependent. Even moderately-sized haematomas can become isodense within 14 days[8] and smaller ones in an even shorter time[7]. After a few months, there may be little to see on CT, and even less that is pathognomonic for previous haemorrhage[12,13]. Certainly no such signs in the region of previous ICH have been assessed for specificity, and it was not possible from the published studies to derive a value for the sensitivity of CT in the identification of ICH. Also, two studies by the same team investigating inter-observer variability in the identification of ICH on CT have shown that not all clinicians and radiologists were equally proficient[47,48] (see 6.3.1). Therefore, although it is likely that, in good hands, CT can identify most, if not all ICH within a few days of ictus, the temporal changes documented can confuse diagnosis, as can tissue calcification and luxury perfusion, meaning that the sensitivity of CT is unlikely to be 100%. However, the difficulty of finding an appropriate gold standard against which to judge CT in the acute phase of stroke (MRI is likely to be more difficult to interpret in this phase, and post mortem introduces selection bias towards the more severe strokes) may mean that determining its sensitivity is an impossible task.

Can we derive a sensitivity for MRI in the identification of ICH?

When MRI first became available, it was clear that identifying ICH was more complicated than with CT, and a number of studies merely described the clinicotopographical changes seen with different sequences. Certainly all sequences are not equally sensitive, for example gradient echo (GRE) sequences (which are not routinely used) have been shown to be highly effective in demonstrating ICH, and for longer periods of time than CT[23,43,44,49]. However, the data on GRE sensitivity in relation to routine structural imaging such as T1 or T2-weighted sequences, and other specialised sequences such as FLAIR, are limited. Also, the data for how long ICH remains visible on MRI is limited. There are data for the late MRI appearances of ICH due to trauma (haemosiderin was still identified in 90% of scans, up to five years after trauma[50], but it is not clear whether the proportion of scans on which ICH remains visible is the same in stroke patients. As radiologists have become more familiar with MRI, studies have been published which demonstrate that it is possible to distinguish haemorrhage, however early. This is useful work but falls short of allowing us to quantify the merit of MRI in relation to CT. The two studies that attempt to do so[38,39] are therefore important, but sample sizes were small, and conclusions drawn far from definitive. The additional problems encountered with MRI of patient acceptability and contraindicated patients are barely addressed. The complete lack of robust data on these subjects considerably weakens our ability to gauge the usefulness of MRI in relation to CT in a non-selected stroke population.

Why has there been such a lack of interest in the sensitivity of CT (and MRI) in ICH?

It may be due in part to the fact that from its introduction in the 1970's, CT was embraced rather uncritically as the new gold standard. Certainly encouraging editorials on the use of CT at the time left little doubt as to how important it was going to be to clinicians[51]. In 1973, in the British Journal of Radiology, Ambrose stated that 'in the overall investigation of cerebrovascular disease, computed tomography will without doubt, come to be an invaluable means of distinguishing between haemorrhage and infarction'[52]. It was certainly the case that CT delivered more information, less

invasively than existing investigations such as air encephalography, angiography or lumbar puncture[53,54]. For MRI, it may be that because it is still being used relatively rarely in acute stroke[5] its sensitivity is not yet seen as an issue. Also, for both CT and MRI, the rapid improvements in scanner technology means the standards against which techniques have to be compared are constantly shifting.

Scientific approach in published studies could be improved

As well as a lack of acknowledgement of the importance of the issue, there is the concern that the paucity of data available may also be due to a general lack of scientific approach in all but a minority of these studies. The majority of studies of CT or MRI in the identification of haemorrhagic stroke are barely more than elaborate descriptions of the images of groups of highly selected patients. Although it is not difficult to see why few studies judged imaging results by another objective standard, prospective study design and blinding of imaging analysis are both extremely important and can easily be addressed. The results of retrospective series of highly selected patients tell us little about how an imaging technique would perform in a non-selected stroke population.

Conclusion

ICH is clearly visible on CT acutely but appearances are time-dependent. Identifying ICH on MRI acutely can be more difficult but is possible, and signs of ICH remain apparent much longer than on CT. Data on sensitivity of CT for the detection of haemorrhage were not available and was extremely limited for MRI.

When there were few options in terms of scanning modalities available to the clinician for the investigation of stroke, it was perhaps excusable not to have a thorough grasp of their accuracy. However, this issue becomes increasingly important as the range of available modalities increase. The dwindling of publications on the identification of ICH on CT in the last two years when unanswered questions remain is also a cause for concern. The clinical neuroimaging literature in stroke is now dominated by studies concerning more advanced neuroimaging strategies (chapter 7). This suggests a trend

to the publication of what is 'fashionable' rather than important and promotes the argument that allocation of radiological resources should not be left in the hands of clinicians and radiologists.

We have attempted to address some of the methodological issues raised in this chapter in our own studies comparing CT and MRI. We also aimed to address some of the questions raised in this chapter such as: what are the best MRI sequences for detecting haemorrhage, and how much better are they? How long does haemorrhage remain visible on MRI after ICH? In what proportion of patients with ICH do signs disappear completely? Are there signs on the scans of such patients that will indicate disappearance? How often does CT show signs of previous haemorrhage? What are the relative sensitivities of CT and MRI in the identification of ICH at different time-points? When does MRI become more useful in detecting ICH than CT? The results of our studies are documented in the following chapter.

Table 1. CT and intracerebral haemorrhage

Study	Date of publication	N of patients	Purpose of study	Assessed by stroke physician?	Readings blinded?
Walshe[55]	76	68	Clinicotopography	No	No
Greenberg[56]	77	6	Clinicotopography	No	No
Lieberman[57]	78	6	ICH in patients with prosthetic heart valves – outcome	No	No
Weisberg[58]	79	232	Clinicotopography (thalamic ganglionic)	Yes	No
Mizukami[59]	81	17	Clinicotopography (putaminal)	No	No
Weisberg[60]	81	12	Clinicotopography (multiple PICH)	Yes	No
Hunger Buhler[61]	83	108	Clinicotopography	No	No
Mayr[62]	83	100	Prognosis	No	No
Garde[63]	83	100	Prognosis, clinicotopography	No	No
Helweg Larsen[64]	84	8	Prognosis	Yes	No
Stein[65]	84	12	Clinicotopography (caudate)	Yes	No
Steiner[66]	84	37	Prognosis	Yes	No
Weisberg[67]	84	8	Clinicotopography (caudate)	Yes	No
Hung[7]	85	31	Prognosis (and serial CT characteristics)	Yes	No
Mori[68]	85	174	Clinicotopography (lacunar)	Yes	No
Weisberg[69]	85	50	Clinicotopography (subcortical lobar)	Yes	No
Tanaka[70]	86	25	Prognosis	Yes	No
Gates[71]	86	5	Clinicotopography	Yes	No
Carbonin[72]	86	5	Clinicotopography	No	No
Dollberg[73]	86	77	Clinicotopography	No	No
Weisberg[74]	86	40	Clinicotopography (pontine)	Yes	No
Dennis[8]	87	5	Serial CT characteristics		
Fieschi[75]	88	104	Prognosis	Yes	No

Study	Date of publication	N of patients	Purpose of study	Assessed by stroke physician?	Readings blinded?
Darby[76]	88	7	Clinicotopography (solitary intraventricular haemorrhage)	Yes	No
Weisberg[77]	88	18	Clinicotopography (occipital)	Yes	No
Iwasaki[78]	88	10	Clinicotopography (lacunar)	No	No
Weisberg[79]	89	25	Clinicotopography (parietal)	Yes	No
Astarloa[80]	89	114	Prognosis	Yes	No
Jayakaimar[81]	89	15	Clinicotopography (solitary intraventricular haemorrhage)	Yes	No
Schutz[21]	90	100	Clinicotopography	Yes	No
Cerillo[82]	90	83	Prognosis	Yes	No
Weisberg[83]	90	100	Clinicotopography	Yes	No
Daverat[20]	91	166	Prognosis	Yes	No
Bogusslavsky[14]	91	15	CT characteristics (haemorrhagic transformation)	No	Yes*
Kreel[13]	91	120	CT characteristics (residual lesions)	No	No
Franke[12]	91	42	CT characteristics (residual lesions)	Yes	No
Franke[19]	92	157	Prognosis	Yes	No
Lisk[84]	94	75	Prognosis	Yes	No
Berlit[85]	94	326	Prognosis	Yes	No
Fujii[11]	94	419	CT characteristics (enlargement of haematoma)	Yes	No
Halpin[17]	94	38	CT characteristics (whether to perform angiography)	No	Yes**
Passero[86]	95	112	Recurrent ICH (incidence)	Yes	No
Bhuvaneswavi[87]	95	87	Prognosis	Yes	No
Lampl[18]	95	279	Prognosis	Yes	No
Mori[88]	95	104	Clinicotopography (thalamic), prognosis	No	No

Study	Date of publication	N of patients	Purpose of study	Assessed by stroke physician?	Readings blinded?
Qureshi[89]	95	182	Prognosis	Yes	No
Mase[90]	95	138	Prognosis	Yes	No
Chaves[91]	96	17	Clinicotopography (cerebellar haemorrhagic transformation)	Yes	No
Kazui[10]	96	204	CT characteristics (enlargement of haematoma)	Yes	No
Zhu[92]	97	206	CT characteristics (comparing diagnoses with angiography)	Yes	No
Chandra[93]	98	45	CT characteristics (comparing diagnoses with angiography)	Yes	No
Butler[94]	98	35	ICH in patients with prosthetic heart valves – outcome	No	No
Gonzalez Duarte[95]	98	22	Recurrent ICH, prognosis	Yes	No

* to other imaging
** to clinical history

Table 2. MRI and intracerebral haemorrhage

Study	Date of publication	N of patients	Purpose of study	CT also performed	Assessed by stroke physician	Readings blinded?
Linfante[29]	99	5	Clinicotopography, hyperacute	No	Yes	No
Offenbacher[45]	96	120	Clinicotopography, asymptomatic haemorrhage	No	No	No
Melhem[23]	98	32	Technical (gradient echo sequence in haemorrhage)	No	No	No
Edelman[24]	86	16	Technical (modification of pulse)	No	Yes	No
Gomori[25]	85	20	Technical	No	No	No
Zimmerman[30]	88	37	Clinicotopography	No	No	No
Shimizu[31]	92	4	Clinicotopography	No	No	No
Liang[26]	99	50	Technical (gradient echo sequence in haemorrhage)	Yes	No	No
Tanaka[42]	99	89	Asymptomatic haemorrhage	Yes	Yes	No
Patel[28]	96	6	Visualise haemorrhage, clinicotopography	Yes	Yes	No
Greenberg[43]	96	25	Asymptomatic haemorrhage	Yes	No	No
Staffen[36]	98	100	Clinical differences between haemorrhagic transformation and PICH	Yes	Yes	No
Steinbrich[39]	90	129	Compare CT and MR	Yes	No	No
Tanaka[46]	88	30	Compare CT and MR	Yes	Yes	No
Schellinger[27]	99	9	Visualise haemorrhage	Yes	Yes	No
Kinoshita[41]	2000	198	Asymptomatic haemorrhage	Yes	Yes	No
Kwa[44]	98	221	Asymptomatic haemorrhage	Yes	Yes	Yes†
Salgado[32]	86	60	Compare CT and MR	Yes	Yes	Yes**
Kertesz[33]	87	175	Compare CT and MR	Yes	Yes	Yes*
Mayer[38]	2000	36	Haemorrhagic transformation serially	Yes	Yes	Yes†
Arias[37]	92	70	Compare CT and MR	Yes	Yes	No
Mohr[34]	95	80	Compare CT and MR	Yes	Yes	Yes**

* blind to other imaging, **blind to clinical history, † blind to both

Table 3. Studies in which patients with ICH were scanned serially with both CT and MRI. Proportion of scans with identified haemorrhage at each time stage.

	Acute phase (%)		Subacute phase (%)		Chronic phase (%)	
	CT	MRI	CT	MRI	CT	MRI
Steinbrich 1990[39] (Haematoma, 129 patients)	93	46	58	97	17	93
Mayer 2000[38] (Haemorrhagic transformation, 36 patients)	0	0	33	38	37	80

Table 4. Studies investing proportion of patients with asymptomatic haemorrhage as evidenced by haemosiderin deposits on MRI

Study	Date	Size (n)	Mean age (years)	Study population	Time of MRI from onset on symptoms	MRI sequences used	Proportion of asymptomatic haemorrhage (%)		
							Non-stroke	ICH	Ischaemic stroke
Greenberg[43]	1996	25	76	'Elderly' patients with lobar haematomas	Within 2 years	T1, T2, proton density		60	
Offenbacher[45]	1996	120	60	Patients with ICH	Within 4 weeks	T1, T2, proton density, GRE in 38 patients		33	
Kwa[44]	1998	221	62	Previous ischaemic stroke, myocardial infarction or peripheral vascular disease	Mean interval 6 months	FSE T2, multiplanar GRE	4		26
Tanaka[42]	1999	89	62	Patients with ICH	Not specified	FSE T2, axial T2 EPI	25.4	56.7	
Kinoshita[41]	2000	198	64	Haemorrhagic or multiple lacunar stroke	Within 4 weeks	FSE T2, GRE-EPI*	5	66	68

FSE – fast spin echo
GRE –gradient echo

1. Chen ZM, Sandercock P, Pan HC, Counsell C, Collins R, Liu LS et al. Indications for early aspirin use in acute ischemic stroke : A combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. Stroke 2000;31:1240-9.

2. Jiang He, Whelton PK, Vu B, Klag MJ. Aspirin and risk of haemorrhagic stroke. A meta-analysis of randomised controlled trials. JAMA 1998;280:1930-5.

3. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81-106.

4. Lindley R, Amayo E, Marshall J, Sandercock PAG, Dennis M, Warlow CP. Hospital services for patients with acute stroke in the United Kingdom: the Stroke Association Survey of Consultant opinion. Age & Ageing 1995;24:525-32.

5. Ebrahim, S. and Redfern, J. Stroke Care - a matter of chance. A national survey of stroke services. 1999. London, The Stroke Association.

6. Franke FL, Ramos LMP, van Gijn J. Development of multifocal haemorrhage in a cerebral infarct during computed tomography. J Neurol Neurosurg Psychiatr 1990;53:531-2.

7. Hung TP,.Lee KY. Small intracerebral haemorrhage: a study of clinical manifestations and CT findings on 31 cases. Annals of the Academy of Medicine, Singapore 1985;14:22-31.

8. Dennis MS, Bamford JM, Molyneux AJ, Warlow CP. Rapid resolution of signs of primary intracerebral haemorrhage in computed tomograms of the brain. BMJ 1987;295:379-81.

9. Wardlaw JM,.Statham PF. How often is haemosiderin not visible on routine MRI following traumatic intracerebral haemorrhage? Neuroradiology 2000;42:81-4.

10. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. Stroke 1996;27:1783-7.

11. Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki O. Hematoma enlargement in spontaneous intracerebral hemorrhage. J Neurosurg 1994;80:51-7.

12. Franke CL, van Swieten JC, van Gijn J. Residual lesions on computed tomography after intracerebral hemorrhage. Stroke 1991;22:1530-3.

13. Kreel L, Kay R, Woo J, Wong HY, Nicholls MG. The radiological (CT) and clinical sequelae of primary intracerebral haemorrhage. British Journal of Radiology 1991;64:1096-100.

14. Bogousslavsky J, Regli F, Uske A, Maeder P. Early spontaneous hematoma in cerebral infarct: is primary cerebral hemorrhage overdiagnosed? Neurology 1991;41:837-40.

15. Rowe CC, Donnan GA, Bladin PF. Intracerebral haemorrhage: incidence and use of computed tomography. BMJ 1988;297:1177-8.

16. Schuetz H, Dommer T, Boedeker RH, Damian M, Krack P, Dorndorf W. Changing pattern of brain hemorrhage during 12 years of computed axial tomography. Stroke 1992;23:653-6.

17. Halpin SFS, Britton JA, Byrne JV, Clifton A, Hart G, Moore A. Prospective evaluation of cerebral angiography and computed tomography in cerebral haematoma. J Neurol Neurosurg Psychiatr 1994;57:1180-6.

18. Lampl Y, Gilad R, Eshel Y, Sarova-Pinhas I. Neurological and functional outcome in patients with supratentorial hemorrhages. A prospective study. Stroke 1995;26:2249-53.

19. Franke CL, van Swieten JC, Algra A, van Gijn J. Prognostic factors in patients with intracerebral haematoma. Journal of Neurology, Neurosurgery & Psychiatry 1992;55 :653-7.

20. Daverat P, Castel JP, Dartigues JF, Orgogozo JM. Death and functional outcome after spontaneous intracerebral hemorrhage. Stroke 1991;22:1-6.

21. Schutz H, Bodecker RH, Damian M, Krack P, Dorndorf W. Age-related spontaneous intracerebral hematoma in a German community. Stroke 1990;21:1412-8.

22. Gunatilake SB. Rapid resolution of symptoms and signs of intracerebral haemorrhage: Case reports. BMJ 1998;316:1495-6.

23. Melhem ER, Patel RT, Whitehead RE, Bhatia RG, Rockwell DT, Jara H. MR imaging of hemorrhagic brain lesions: a comparison of dual- echo gradient- and spin-echo and fast spin-echo techniques. AJR 1998;797-802.

24. Edelman RR, Johnson K, Buxton R, Shoukimas G, Rosen KR, Davis KR. MR of hemorrhage: a new approach. Am J Neuroradiol 1986;7:751-6.

25. Gomori JM, Grossman RI, Goldberg HI, Zimmerman RA, Bilanuk LT. Intracranial haematomas: imaging by high filed MR. Radiology 1985; 157: 87-93.

26. Liang L, Korogi Y, Sugahara T, Shigematsu Y, Okuda T, Ikushima I et al. Detection of intracranial hemorrhage with susceptibility-weighted MR sequences. Ajnr: American Journal of Neuroradiology 1999;20:1527-34.

27. Schellinger PD, Jansen O, Fiebach JB, Hacke W, Sartor K. A standardized MRI stroke protocol: comparison with CT in hyperacute intracerebral hemorrhage. Stroke 1999;30:765-8.

28. Patel MR, Edelman RR, Warach S. Detection of hyperacute primary intraparenchymal hemorrhage by magnetic resonance imaging. Stroke 1996;27:2321-4.

29. Linfante I, Llinas RH, Caplan LR, Warach S. MRI features of intracerebral hemorrhage within 2 hours from symptom onset. Stroke 1999;30:2263-7.

30. Zimmerman RD, Heier LA, Snow RB, Liu DPC, Kelly AB, Deck MDF. Acute intracranial hemorrhage: Intensity changes on sequential MR scans at 0.5 T. American Journal of Roentgenology 1988;150:651-61.

31. Shimizu T, Naritomi H, Kuriyama Y, Sawada T. Sequential changes of sodium magnetic resonance images after cerebral hemorrhage. Neuroradiology 1992;34:301-4.

32. Salgado ED, Weinstein M, Furlan AJ, Modic MT, Beck GJ, Estes M et al. Proton magnetic resonance imaging in ischemic cerebrovascular disease. Ann.Neurol. 1986;20:502-7.

33. Kertesz A, Black SE, Nicholson L, Carr T. The sensitivity and specificity of MRI in stroke. Neurology 1987;37:1580-5.

34. Mohr JP, Biller J, Hilal SK, Yuh WTC, Tatemichi TK, Hedges S. Magnetic resonance versus computed tomographic imaging in acute stroke. Stroke 1995;26:807-12.

35. Steinbrich W, Friedmann G, Pawlik G, Bocher-Schwarz HG, Heiss WD. MR of ischaemic brain diseases. A comparison with CT,PET and angiographic results. ROFO: Fortschritte auf dem Gebiete der Rontgenstrahlen und der nuklearmedizin. 1986;145:173-81.

36. Staffen W, Trinka E, McCoy M, Iglseder B, Unterrainer J, Ladurner et al. A comparison of neuroimaging and clinical findings in 100 patients with haemorrhagic infarction and intracerebral haematoma. Aktuelle Neurologie 1998;25:69-73.

37. Arias M, Requena I, Pereiro I, Amigo ME, Ventura M, Quintans L et al. [CT vs MRI in the diagnosis of acute stroke]. [Spanish]. Archivos de Neurobiologia 1992;55:50-6.

38. Mayer TE, Schulte-Altedorneburg G, Droste DW, Bruckmann H. Serial CT and MRI of ischaemic cerebral infarcts: Frequency and clinical impact of haemorrhagic transformation. Neuroradiology 2000;42:233-9.

39. Steinbrich W, Gross-Fengels W, Krestin GP, Heindel Schreier WG. MRI examinations of intracranial hmatomas. an analysis of its sensitivity evolution and source of bleeding. Rofo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin 1990; 152:534-43.

40. Martin PJ, Young G, Enevoldson TP, Humphrey PR. Overdiagnosis of TIA and minor stroke: experience at a regional neurovascular clinic. QJM 1997;90:759-63.

41. Kinoshita T, Okudera T, Tamura H, Ogawa T, Hatazawa J. Assessment of lacunar hemorrhage associated with hypertensive stroke by echo-planar gradient-echo T2*-weighted MRI. Stroke 2000;31:1646-50.

42. Tanaka A, Ueno Y, Nakayama Y, Takano K. Small chronic haemorrhages and ischaemic lesions in association with spontaneous intracerebral haematomas. Stroke 1999;30:1637-42.

43. Greenberg SM, Finklestein SP, Schaefer PW. Petechial hemorrhages accompanying lobar hemorrhage: detection by gradient-echo MRI. Neurology 1996;46:1751-4.

44. Kwa VIH, Franke CL, Verbeeten Jr B, Stam J. Silent intracerebral microhaemorrhages in patients with ischaemic stroke. Ann Neurol 1998;44:372-7.

45. Offenbacher H, Fazekas F, Schmidt R, Koch M, Fazekas G, Kapeller P. MR of cerebral abnormalities concomitant with primary intracerebral haematomas. Am J Neuroradiol 1996;17:573-8.

46. Tanaka T, Sakai T, Uemura K, Teramura A, Fujishima I, Yamamoto T. Magnetic resonance imaging in the acute stage of cerebrovascular disease - Clinical comparison with computed tomography. Neurologia Medico-Chirurgica 1988;28:974-80.

47. Schriger DL, Kalafut M, Starkman S, Krueger M, Saver JL. Cranial computed tomography interpretation in acute stroke: physician accuracy in determining eligibility for thrombolytic therapy. JAMA 1998;279:1293-7.

48. Kalafut M, Starkman S, Saver J, Villablanca P, Schriger D. Early infarct and haemorrhage interpretation by emergency physicians: implications for thrombolytic therapy. Stroke 1997;28:270.

49. Liang L, Korogi Y, Sugahara T, Shigematsu Y, Okuda T, Ikushima I et al. Detection of intracranial hemorrhage with susceptibility-weighted MR sequences. Ajnr: American Journal of Neuroradiology 1999;20:1527-34.

50. Wardlaw JM,.Statham PF. How often is haemosiderin not visible on routine MRI following traumatic intracerebral haemorrhage? Neuroradiology 2000;42:81-4.

51. Anonymous. Non-invasive investigations of the brain. BMJ 1975;2:295-6.

52. Ambrose J. Computerised transverse axial scanning (tomography): part 2: clinical application. Br.J.Radiol. 1973;46:1023-47.

53. Britton M, Hultman E, Murray V, Sjoholm H. The diagnostic accuracy of CSF analyses in stroke. Acta Med.Scand. 1983;214:3-13.

54. Isherwood I, Rutherford RA, Pullen BR. Computerized tomography of brain. Br.Med.J. 1975;2:746-7.

55. Walshe TM, Hier DB, Davis KR. The diagnosis of hypertensive intracerebral hemorrhage: the contribution of computed tomography. Computerized tomography 1977;1:63-9.

56. Greenberg JO,.Skubick DL. Unexpected brain hemorrhages and the value of computerized tomography. Computerized tomography 1977;1:349-57.

57. Lieberman A, Hass WK, Pinto R, Isom WO, Kupersmith M, Bear G et al. Intracranial hemorrhage and infarction in anticoagulated patients with prosthetic heart valves. Stroke 1978;9:18-24.

58. Scott WR, Paul FJ, Davis KR, Schnur JA. Computerized axial tomography of intracerebral and intraventricular hemorrhage. Radiology 1974;112:73-80.

59. Mizukami M, Nishijima M, Kin H. Computed tomographic findings of good prognosis for hemiplegia in hypertensive putaminal hemorrhage. Stroke 1981;12:648-52.

60. Weisberg L. Multiple spontaneous intracerebral hematomas: clinical and computed tomographic correlations. Neurology 1981;31:897-900.

61. Hungerbuhler MD, Regli MD, Van Melle PD, Bogousslavsky J. Spontaneous intracerebral haemorrhages (SICHs). Clinical and CT features; immediate evaluation of prognosis. Schweizer Archiv fur Neurologie, Neurochirurgie und Psychiatrie 1983;132:13-27.

62. Mayr U, Bauer P, Fischer J. Non-traumatic intracerebral haemorrhage. Prognostic implications of neurological and computer-tomographical findings in 100 consecutive patients. Neurochirurgia 1983;26:36-41.

63. Garde A, Bohmer G, Selden B, Neiman J. 100 cases of spontaneous intracerebral haematoma. Eur Neurol 1983;22:161-72.

64. Helweg-Larsen S, Sommer W, Strange P, Lester J, Baysen G. Prognosis for patients treated conservatively for spontaneous intracerebral haematomas. Stroke 1984;15:1045-8.

65. Stein RW, Kase DB, Hier DB, Caplan LR, Mohr JP, Hemmati M. Caudate hemorrhage. Neurology 1984;34:1549-54.

66. Steiner I, Gomori JM, Melamed E. The prognostic value of the CT scan in conservatively treated patients with intracerebral hematoma. Stroke 1984;15:279-82.

67. Weisberg L. Caudate hemorrhage. Archives of Neurology 1984;41:971-4.

68. Mori E, Tabuchi M, Yamadori A. Lacunar syndrome due to intracerebral hemorrhage. Stroke 1985;16:454-?

69. Weisberg L. Subcortical lobar intracerebral haemorrhage: clinical-computed tomographic findings. J Neurol Neurosurg Psychiatr 1985;48:1078-84.

70. Tanaka Y, Furuse M, Iwasa H, Masuzawa T, Saito K, Sato F. Lobar intracerebral hemorrhage: etiology and a long-term follow-up study of 32 patients. Stroke 1986;17:51-7.

71. Gates PC, Barnett HJM, Vinters HV, Simonsen RL, Siu K. Primary intraventricular hemorrhage in adults. Stroke 1986;17:872-7.

72. Carbonin C, Toso V, Cagnin G, Antonini D. Primary brain stem haemorrhages: clinico-radiological considerations on five cases observed. Neurochirurgia 1986;29:53-7.

743 Dollberg S, Rosin AJ, Fisher D. A new look at the natural history and clinical features of intracerebral haemorrhage: a clinical CT scan correlation. Gerontology 1986;32:211-6.

74. Weisberg L. Primary pontine haemorrhage: clinical and computed tomographic correlations. J Neurol Neurosurg Psychiatr 1986;49:346-52.

75. Fieschi C, Carolei A, Fiorelli M, Argentino C, Bozzao L, Fazio M. Changing prognosis of primary intracerebral hemorrhage: results of a clinical and computed tomographic follow-up study of 104 patients. Stroke 1988;19:192-5.

76. Darby DG, Donnan GA, Saling MA, Walsh KW, Bladin PF. Primary intraventricular haemorrhage: clinical and neuropsychological findings in a prospective series. Neurology 1988;38:68-75.

77. Weisberg LA,.Stazio A. Occipital lobe hemorrhages; clinical-computed tomographic correlations. Computerized Medical Imaging & Graphics 1988;12:353-8.

78. Iwasaki Y,.Kinoshita M. Lacunar syndrome and intracerebral hemorrhage: clinico-computed tomographic correlations. Computerized Medical Imaging & Graphics 1988;12:359-63.

79. Weisberg LA,.Stazio A. Nontraumatic parietal subcortical hemorrhage: clinical-computed tomographic correlations. Computerized Medical Imaging & Graphics 1989;13:355-61.

80. Astarloa R, Jimenez-Scrig A, Gimeno A. [Prognostic value of CAT scanning in spontaneous supratentorial cerebral hemorrhage. Multivariate study in 114 patients]. [Spanish]. Archivos de Neurobiologia 1989;52:234-8.

81. Jayakumar PN, Taly AB, Bhavani UR, Arya BY, Nagaraja D. Prognosis in solitary intraventricular haemorrhage. Clinical and computed tomographic observations. Acta Neurol Scand 1989;80:1-5.

82 Cerillo A, Villano M, Vizioli L, Narciso N, Tedeschi E, Bucchiero A et al. Intracerebral haemorrhage: criteria for prognosis on the grounds of clinical and CT data. Journal of Neurosurgical Sciences 1990;34:123-36.

83. Weisberg LA, Stazio A, Elliott D, Shamsnia M. Putaminal hemorrhage: clinical-computed tomographic correlations. Neuroradiology 1990;32:200-6.

84. Lisk DR, Pasteur W, Rhoades H, Putnam RD, Grotta JC. Early presentation of hemispheric intracerebral hemorrhage: prediction of outcome and guidelines for treatment allocation. Neurology 1994;44:133-9.

85. Berlit P,.Tornow K. Outcome of intracerebral hemorrhage: clinical and CT findings in 326 patients. Eur J Neurol 1994;1:29-43.

86. Passero S, Burgalassi L, D'Andrea P, Battistini N. Recurrence of bleeding in patients with primary intracerebral hemorrhage. Stroke 1995;26:1189-92.

87. Dandapani BK, Suzuki S, Kelley RE, Reyes-Iglesias Y, Duncan RC. Relation between blood pressure and outcome in intracerebral hemorrhage [see comments]. Stroke 1995;26:21-4.

88. Mori S, Sadoshima S, Ibayashi S, Fujishima M, Iino K. Impact of thalamic hematoma on six-month mortality and motor and cognitive functional outcome. Stroke 1995;26:620-6.

89. Qureshi AI, Safdar K, Weil J, Barch C, Bliwise DL, Colohan AR et al. Predictors of early deterioration and mortality in black Americans with spontaneous intracerebral hemorrhage. Stroke 1995;26:1764-7.

90. Mase G, Zorzon M, Biasutti E, Tasca G, Vitrani B, Cazzato G. Immediate prognosis of primary intracerebral hemorrhage using an easy model for the prediction of survival. Acta Neurol Scand 1995;91:306-9.

91. Chaves CJ, Pessin MS, Chung CS, Amarenco P, Breen J, Fine J. Cerebellar haemorrhagic infarction. Neurology 1996;46:346-9.

92. Hsiang JN, Zhu XL, Wong LK, Kay R, Poon WS. Putaminal and thalamic hemorrhage in ethnic chinese living in Hong Kong. Surgical Neurology 1996;46:441-5.

93. Eshwar Chandra N, Khandelwal N, Bapuraj JR, Mathuriya SN, Vasista RK, Kak VK et al. Spontaneous intracranial hematomas: role of dynamic CT and angiography. Acta Neurol Scand 1998;98:176-81.

94. Butler AC,.Tait RC. Restarting anticoagulation in prosthetic heart valve patients after intracranial haemorrhage: A 2-year follow-up. British Journal of Haematology 1998;103:1064-6.

95. Gonzalez-Duarte A, Cantu C, Ruiz-Sandoval JL, Barinagarrementeria F. Recurrent primary cerebral hemorrhage: frequency, mechanisms, and prognosis. Stroke 1998;29:1802-5.

5 Changes Over Time In CT And MRI In The Detection Of Intracerebral Haemorrhage

5.1 Introduction

More information is required on the relative merits of CT and MRI in the identification of intracerebral haemorrhage

Chapter 2 demonstrated the potential inaccuracy of the proportions of stroke subtypes reported in stroke incidence studies because of inadequate scanning. Chapter 3 highlighted the potential harm that could occur if patients with intracerebral haemorrhage (ICH) are given antithrombotic drugs. Chapter 4 highlighted how limited the data are on the sensitivity of CT and MRI in the detection of ICH. It is evident that not enough is known about the relative merits of CT and MRI in the detection of ICH.

Many questions remain unanswered by the existing literature. Small studies[1,2] have demonstrated that haemorrhage on CT will become indistinguishable from ischaemic stroke within days. Were the patients in these studies rare exceptions? How representative of the stroke population are they? MRI can identify haemorrhage at some time after ictus[3,4], but for how long after? Does MRI reliably identify *all* old haemorrhage? Detection of old haemorrhage on MRI relies on the paramagnetic effects of the haemoglobin breakdown product, haemosiderin, which is thought to persist in macrophages at the edges of old haematomas indefinitely. However, pathological studies have demonstrated that not all haematomas form haemosiderin[5]. Some, especially in babies, form haematoidin which lacks magnetic properties, so theoretically would not produce the characteristic MRI features of old haemorrhage. The proportion of haematomas in which this may occur however, is unknown, as no systematic follow-up study has been performed in haemorrhagic stroke either with pathology or MRI. Is the situation the same as for the persistence of ICH after trauma[6]? How much better at detecting late haemorrhage is MRI when directly compared to CT? If MRI is better, what difference does it make? Does knowing a patient previously had an ICH alter their subsequent management?

The potential scale of the problem

According to the Stroke Association Survey (SAS), about 85% of patients with stroke symptoms are admitted to UK hospitals[7], thereby leaving 15% of patients with stroke symptoms being dealt with in the community. This represents around 22000 people according to SAS estimates, some of which will present to hospital as outpatients, and the rest will be managed by their General Practitioners. These patients are likely to be considered for aspirin or anticoagulation for secondary prevention. What proportion of this population of perhaps 22000 people may have had ICH?

Prospective observational studies undertaken at the Western General Hospital

To investigate the duration of signs of haemorrhage on MRI, the relative sensitivities of various MRI sequences in the detection of haemorrhage, the proportion of patients presenting with minor stroke who have had ICH, the relative sensitivities of CT and MRI in the detection of ICH in such a population, the acceptability of each type of scanning for the patients, and the effect of scan findings upon clinical decision making , we performed two prospective observational studies.

- *The late haemorrhage study.* The aim was to investigate the proportion of haemorrhages and the length of time haemorrhage remains visible on MRI following primary intracerebral haemorrhage (PICH), and the relative sensitivities of various MR imaging sequences. The hypotheses were that haemorrhage would persist in a similar proportion of patients to that following head injury (about 90%[6]), and that not all MRI sequences would be equally sensitive.
- *The CT versus MRI study.* The aim was to investigate the relative sensitivities of CT and MRI in the detection of haemorrhage in a population of patients with milder stroke symptoms, who often do not present until weeks after their event. The hypotheses were: that a proportion of these patients would have had ICH, that MRI would identify more ICH than CT; that a proportion of patients would not tolerate MRI: and that knowledge of a previously unknown ICH would alter clinical decision-making.

5.2 The Late Haemorrhage Study

5.2.1 Methods

Patient recruitment

Between February 1991 and February 1999, patients presenting with acute stroke symptoms and in whom PICH had been identified on CT scan, were retrospectively identified from the local stroke register. The stroke register at the Western General Hospital in Edinburgh recruited inpatients from 1991 to 1999 and outpatients from 1994 to 1999. Patients were recruited consecutively as far as possible. Each patient was examined prospectively by a Stroke Physician or Clinical Fellow in Stroke Medicine, and underwent regular follow-up by questionnaire and telephone. Each case was discussed with at least one other Stroke Physician for consensus on diagnosis. Patients who had had the PICH at least three months prior to the start of the study in June 1999 and were still alive, were invited to attend for a follow-up MRI scan. Before contacting patients directly, permission was sought from their Stroke Physician and their General Practitioner. Any patients with contraindications to MRI (e.g. pacemaker, intracranial aneurysm clip) were excluded from the study. Approval for the study was obtained from the local ethics committee.

Image acquisition

Patients who attended for MRI underwent routine structural imaging using an Elscint 2T Prestige scanner. The following images were performed: T1-weighted sagittal images (T1-WI, TR 500 ms, TE 12 ms, 1 NEX), fast spin-echo (FSET2, TR 5000 ms, TE 96 ms, 1 NEX) and spin echo T2-weighted (SET2), FSE proton density (PD, TR 2300 ms, 16 ms, 1 NEX), fluid attenuated inversion recovery (FLAIR, TR 6000 ms, TE 2000 ms, TI 126 ms, 1 NEX) and gradient-echo (GRE, TR 510 ms, TE 18 ms, 2 NEX) axial sequences. Slice thickness was 5 mm, slice gap was 5 mm, 22.0 x 22.0 field of view, 256 x 128 matrix. Total

scanning time was about 30 minutes (from the time the patient was put in the scanner to coming out). See Appendix IV for a glossary of imaging parameter terms.

Image analysis

MRI images were read by one neuroradiologist, with no knowledge of the patient's clinical signs (other than they had had a PICH somewhere in the brain, sometime in the past) or baseline CT, or the time elapsed from the original event. MRI scans were read independently of the original CT scan. MR sequences were read independently of each other in batches of the same sequence, with a suitable interval of time (minimum of two weeks) in between batches to prevent recall of the findings of other sequences. The baseline CT scans were also retrieved and read after the MR images were read to identify the presenting PICH.

Data recorded

From the baseline CT scan, the following were noted:

- The sites of the haematoma(s) (primary lesions);
- The estimated volume of haematoma (maximum length and width, multiplied by the slice thickness (mm) and the number of slices on which the haematoma was seen);
- Any other findings (secondary lesions).

Lesions identified on follow-up MRI sequences were coded as:

- Visible as haemorrhage (all lesions were documented, if there was more than one haematoma, the largest haematoma was recorded as the primary lesion. If there was evidence of haematoma and infarct together, the lesion was documented as haematoma first);
- Visible as infarct (if there was more than one infarct, the largest infarct was recorded as the primary infarct);
- Uncertain;
- Not visible.

Scans were also coded for atrophy, leukoariosis, enlarged perivascular spaces (on FSE T2), small vessel disease (FLAIR), and microhaemorrhage in the basal ganglia or elsewhere (GRE).

Any secondary lesions seen, (i.e. that had appeared in the time after the original CT scan) were documented. This was done matching up information in the database, not at time of reading scans. If an MRI scan demonstrated multiple haematomas, it was compared directly with the original CT to identify which was the primary lesion and which the (asymptomatic) secondary lesion.

Data analysis

Results were entered into a Microsoft Excel spreadsheet, an SPSS (Statistical package for Social Sciences) database, and analysed with simple descriptive statistics.

5.2.2 Results

Patients, tolerability, inadequate scans

Seventy-three patients were identified from the stroke register. From the the initial permission letters sent to General Practitioners, 20 patients were thought unfit for further scanning or had died. 53 patients were invited to return for follow-up MRI scanning. One patient died before attending, one had aneurysm clips, 13 patients declined or were unable to attend, 11 did not attend for their appointments, one patient attended but was claustrophobic. A total of 26 people were scanned with both CT and MRI. Three people had two primary haematomas on their CT scan, therefore the MR results of a total of 29 haematomas were documented. Of a total of 156 MRI scans, three were uninterpretable (two FSET2 sequences, one FLAIR sequence) due to patient movement or because the imaging had to be discontinued due to patient intolerance.

Baseline characteristics of patients

The clinical status of the original 73 patients identified, according to the the OCSP classification, were: 11 total anterior circulation strokes (TACS), 30 partial anterior circulation strokes (PACS), 6 lacunar strokes (LACS), 15 posterior circulation strokes (POCS) and 11 in whom it was not possible to make a classification. In the group of 26 patients who were ultimately scanned, there were 3 TACS, 12 PACS, 2 LACS, 5 POCS, and 4 that were unclassifiable. At the time of their original PICH, the median age of the patients who attended for scanning was 66 years (range 39 - 83). At the time of follow-up MR scanning, their median age was 69 years (range 42-87).

Distribution of haematomas of CT

The mean haematoma volume was 23.9cm^3, the median haematoma volume was 18cm^3 (range 1-80) (table 1). Haematomas were distributed as follows: five in the frontal lobe; 10 in the basal ganglia; two in the thalamus; four in the parietal lobe; two in the temporal lobe; three in the occipital lobe; one in the occipito-parietal lobe; two in the brainstem/cerebellum (table 2).

Findings on follow-up MRI sequences

The proportion of haemorrhage identified varied between the five MRI sequences. GRE identified all haemorrhages (100%). T1 identified haemorrhage on 28/29 (97%), FSET2 identified 27/29 (93%), PD identified 17/29 (59%), and FLAIR failed to identify any lesions as old haemorrhage (0%) (table 3).

The longest period from CT to follow-up MRI was 100.3 months (8.4 years), and concerned a right hemisphere 1cm^3 basal ganglia lacunar haemorrhage that was still visible on T1, T2 and GRE sequences. No patient or brain imaging features, such as timing of scan, age of patient, or size of haematoma distinguished the haematomas that did remain visible from those that did not.

Any secondary lesions seen on initial CT are documented in table 4, with the corresponding findings on follow-up MRI. In 19/26 patients (73%), an ischaemic infarct not documented on the initial CT was seen on at least one sequence of follow-up MRI. In 12/26 (46.2%), there was evidence of definite new, presumably asymptomatic haemorrhage since the original CT.

Other findings on follow-up MRI are documented in table 5. GRE identified haemorrhagic spots in the basal ganglia and cortex in the same eight (28%) of patients. FLAIR identified small vessel disease on 18 (62%). FSET2 identified enlarged perivascular spaces on 16 (55%). Atrophy was identified on 20 (69%) of scans.

5.3 The CT Versus MRI Study

5.3.1 Methods

Patient recruitment

Between August 1998 and July 2000, patients presenting to the Western General Hospital with minor stroke symptoms (defined as symptoms lasting greater than 24 hours but causing little or no functional impairment), or presenting more than five days after onset of stroke symptoms regardless of stroke severity, were scanned on the day of presentation with CT and MRI. The majority of the population recruited were outpatients presenting to a neurovascular clinic, and all were assessed prior to scanning by a consultant stroke physician, or a clinical research fellow in stroke medicine. Patients were classified according to the Bamford classification[8] (appendix I), and the Canadian Neurological Score (CNS, a neurological disability score ranging from 1.5 indicating very severe stroke, to 10 indicating little or no residual disability, appendix V)[9]. Medically unstable patients, and patients with contraindications to MRI (e.g. pacemaker, intraocular metal, intracranial aneurysm clips) were excluded.

Image acquisition

The order of scanning was determined by availability of each scanner, i.e. not randomly. CT was performed using a GE spiral scanner (17 images, 5mm slice thickness, total scan time from patient going into and coming out the scanner was about 7 minutes). MR imaging was performed on two scanners; up to October 1999 using an Elscint Prestige 2T scanner, and from January 2000, using a GE 1.5 Signa Horizon LX scanner. Patients underwent routine structural MR imaging and the imaging parameters for the two scanners were as follows: on the Elscint scanner T1-weighted sagittal images (TR 500 ms, TE 12 ms, 1 NEX), T2-weighted fast spin echo (TR 5000 ms, TE 96 ms, 1 NEX), proton density (TR 2300 ms, 16 ms, 1 NEX), FLAIR (TR 6000 ms, TE 2000 ms, TI 126 ms, 1 NEX), and gradient echo (TR 510 ms, TE 18 ms, 2 NEX) axial images. Slice thickness was 5 mm,

slice gap was 5 mm, 22.0 x 22.0 field of view, 256 x 128 matrix. On the GE Signa Horizon scanner TI sagittal images (TR 440 ms, TE 9 ms, 2 NEX), T2-weighted axial (TR 6300 ms, TE 106 ms, 2 NEX), proton density (TR 2000 ms, TE 9.8 ms, 4 NEX), FLAIR (TR 10002 ms, TE 147 ms, TI 2500 ms, 1 NEX), gradient echo (TR 2599 ms, TE 80, 4 NEX). Slice thickness was 5mm, slice gap was 5 mm, 24.0 x 24.0 field of view, 256 x 256 matrix.

Patient preference questionnaire

Following completion of scanning, patients were asked to complete a questionnaire on the acceptability of both scanning procedures (appendix VI). They were asked what type of scan they had undergone first, which scanner they preferred, and whether they would have either CT or MRI again if they had to. They were also asked to make any additional comments.

Image analysis

CT and MRI scans were read independently of each other by one neuroradiologist, using forms generated using Microsoft Access on which was a brief clinical history (appendix VII). Scans were classified as showing:

- Recent (ischaemic) infarct;
- Recent infarct with haemorrhagic transformation (HTI);
- Recent haemorrhage;
- Old lesion probable infarct;
- Old lesion probable haemorrhage;
- Multiple periventricular lucencies;
- Cortical atrophy;
- Another diagnosis (e.g. tumour);
- No abnormality.

'Recent' was taken to mean consistent with the duration of symptoms given in the brief clinical history. 'Old' was taken to mean a lesion that appeared older than the clinical history.

The effect of scan results on clinical decision-making

Nine physicians with an interest in stroke were presented with a selection of anonymised histories of scanned patients, initially without imaging results. They were asked for their strategy for secondary prevention for the patient in terms of the use of antiplatelet drugs, anticoagulants, or referral for carotid endarterectomy. On the decision forms were details of ECG, echocardiography or carotid Duplex scanning if these had been performed (appendix VIII). On each occasion, each physician was asked to rate their confidence in their diagnosis in terms of percentage for: stroke versus non-stroke, haemorrhage versus ischaemic stroke, and cause of haemorrhage or ischaemic stroke. They were not required to state a definitive diagnosis. They were initially instructed to decide on a management strategy assuming no neuroimaging would be performed. After a number of weeks (not less than four), they were presented with the histories (each physician being given the same histories as they had had originally) along with a brief report of the CT findings, and asked again for their secondary prevention strategies. After a number of weeks, they were again given their respective patient histories, this time with results of MRI.

Data analysis

Data on scan findings, and doctor's decisions were entered along with baseline characteristics, brief histories, and relevant associated investigations onto a password-protected Access database. The proportions of haemorrhage and HTI on CT and MRI were analysed with simple descriptive statistics and confidence intervals. The effect on doctor's decisions was determined by the number of altered decisions; a prospective power calculation identified that, assuming the CT result altered management in 10% of patients, and MRI altered management in 10% of patients in whom the CT result is already known, a study population of 225 patients would have an 80% power to detect this 10% difference at the 95% significance level. Differences in the degree of certainty of diagnosis were analysed using a single sample t-test, differences between doctors were analysed with ANOVA, using SPSS. The neuroradiolologist reading the scans completed a small sample

of scans twice, and two Stroke Physicians also completed a small sample of decisions twice in order to check intra-observer variation.

5.3.2 Results

Patient baseline characteristics, and acceptability of scanning

232 patients were recruited, MRI was not performed in 4 (1.7%) patients (three patients were claustrophobic, one was too large for the scanner). A total of 228 patients had both CT and MRI. No images were uninterpretable.

The mean age of the population was 67.5 years, median age 68 years (range 35 to 89 years). The mean CNS was 9.5, median CNS was 9.5 (range 5.5 to 10). The mean time from onset of stroke symptoms to scanning was 21.7 days, median time 20 days (range 2 to 112) (table 6). According to the Bamford classification, there were 95 (41.7%) PACS, 73 (32%) LACS, 36 (15.8%) POCS, and in 24 (10.5%), it was not possible to define a subtype (table 7). There were no patients with TACS. Prior to scanning (on presentation), 144 (63.2%) were on aspirin, three (1.3%) were on warfarin, and ten (4.3%) were in atrial fibrillation.

Findings on CT and MRI

Table 8 documents the main findings on CT and MRI. Note that more than one type of lesion could be found on the same scan (e.g. many scans with a recent infarct also had cortical atrophy). The findings on the images of the 228 patients are documented in a hierarchy i.e. PICH, HTI and recent infarct are documented in favour of any other diagnosis. Other diagnoses are documented in the table only if they were the only significant finding on the scan. The findings with regards haemorrhage and tumours are given below. Details of CT and MRI findings with regards to recent infarction are documented in section 6.3.4.

Recent haemorrhage

MRI identified recent PICH in 8 (3.5%, 95% CI 1.5-6.8%) patients. CT agreed in only 2 (0.9%, 95% CI 0.1-3.1%) cases. Corresponding findings on CT when recent haemorrhage was not identified were: recent infarct (5 patients), and old lesion probable infarct (1 patient). Thus in patients with recent haemorrhage identified on MRI, CT missed the diagnoses in 6/8 (75%) (figures 1 to 6).

Recent infarct with haemorrhagic transformation (HTI)

MRI identified HTI in 15 (6.6%, 95% CI 3.7-10.6%) patients. The extent of haemorrhagic changes seen varied from minor petechial spots to frank haematoma. CT agreed in only 2 (0.9%, 95% CI 0.1-3.1%) cases. Corresponding findings on CT when HTI was not identified were: recent haemorrhage (1 patient), recent infarct (10 patients), old lesion, probable infarct (1 patient), multiple periventricular lucencies and cortical atrophy only (1 patient). CT therefore missed the haemorrhagic changes seen on MRI in 12/15 (80%) (figures 7 to 18).

CT identified HTI on one scan that was interpreted as recent infarct only on MRI. On review of both scans, The CT result was judged to be incorrect, the changes seen on imaging being due to the contrast of normal cortex next to infarct, as there was no evidence of haem on GRE MRI.

Timing of scans identifying haemorrhage

The range of times from onset of symptoms to scan for both CT and MRI in patients found to have either recent haemorrhage or HTI along with clinical presentation is documented in table 9. The shortest time from onset of symptoms to scan when HTI was missed on CT was five days, and the shortest time PICH was missed on CT was 11 days (although this may have been sooner if scans were performed earlier). The two patients in whom CT correctly identified recent haemorrhage were scanned on nine and 14 days after stroke.

Signs of previous haemorrhage

Signs suggestive of an old lesion that was probably haemorrhagic were seen on 15 (6.6%, 95% CI 3.7-10.6%) of MRI scans but no CT scans. They were the only significant findings in five patients (2.3%). In the remaining ten, these signs were seen alongside signs of recent infarction (eight patients), and HTI (two patients).

Tumours

CT scans identified 5 tumours in 228 patients (1.7%): 2 intra-axial, 3 extra-axial (three meningiomas; two of which were incidental, less than 1cm in diameter, and not responsible for symptoms). MRI also identified the 2 intra-axial tumours and the symptomatic meningioma, but not the two incidental meningiomas.

Figures. Missed haemorrhages

Unless otherwise stated, the CT scan is on the left, T2-weighted MRI centre and where available, gradient echo MRI on right.

The relevant area of hypodensity on CT presumed to be ischaemic infarct is highlighted with an arrow, and the corresponding area on MRI of hyperintensity surrounded by dark rim, or dark rim alone is marked by arrows on MRI.

Figure 1. 72 year old man with left homonymous hemianopia, scanned 28 days after onset of symptoms.

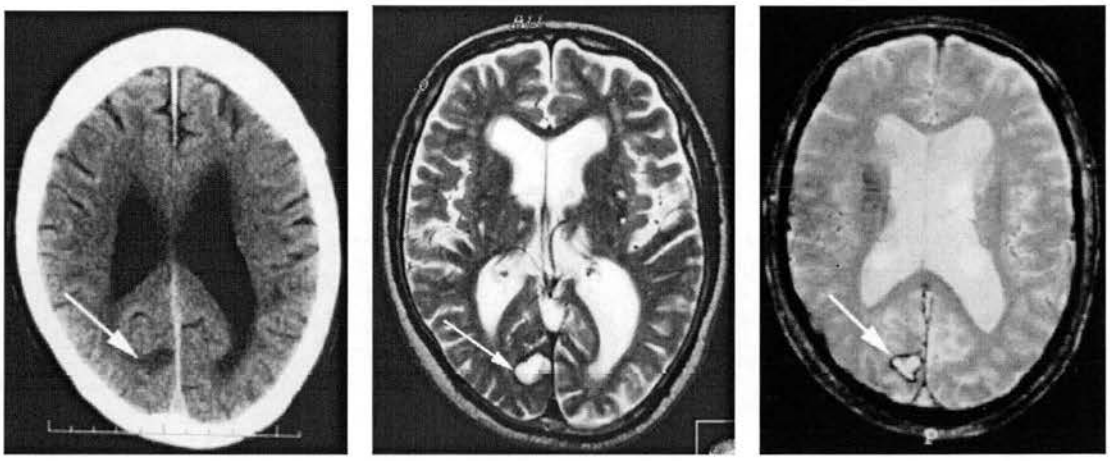


Figure 2. 69 year old man with mild right hemiparesis, residual mild facial weakness. Scanned 13 days after onset of symptoms.

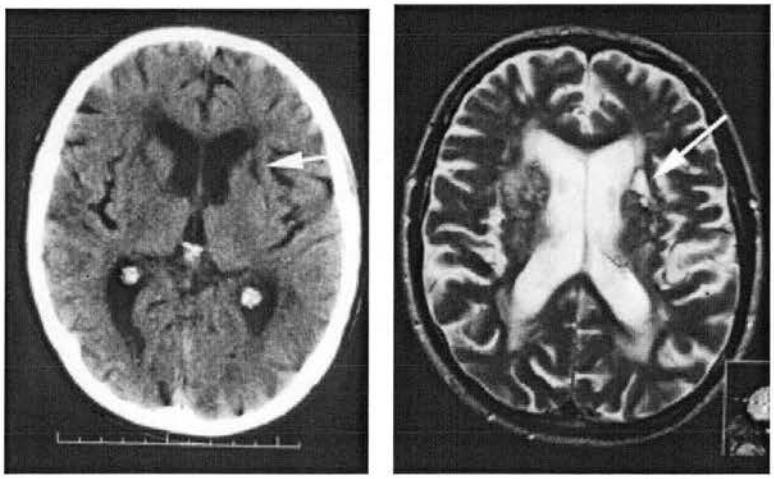


Figure 3. 60 year old man with right hemiparesis and right facial numbness, residual reduced fine finger movements. Scanned 21 days after onset of symptoms.

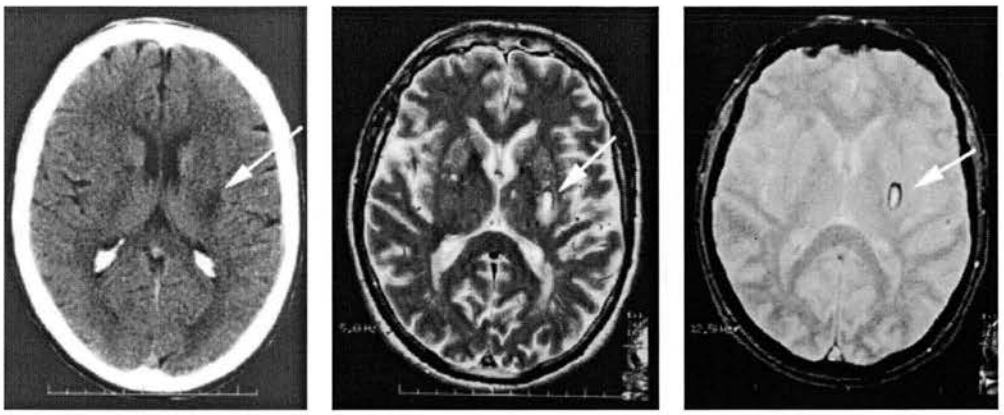


Figure 4. 69 year old woman with right arm and hand numbness lasting 12 days. Scanned14 days from onset of symptoms.

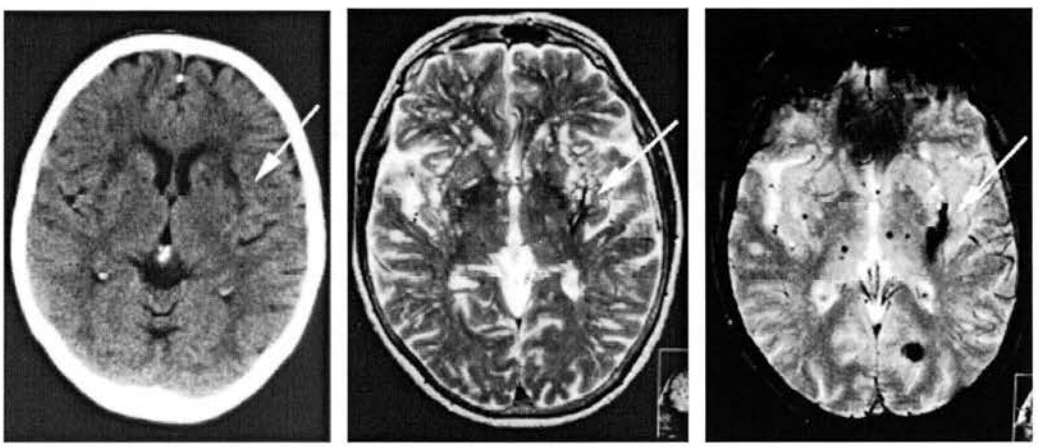


Figure 5. 51 year old woman with ataxia, blurring of vision, no residual signs. Scanned 17 days from onset of symptoms.

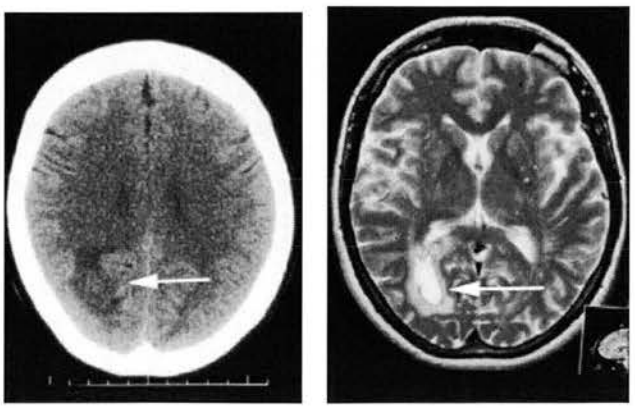


Figure 6. 68 year old man with right hemiparesis and dysphasia, mild weakness persisting. Scanned at 11 days.

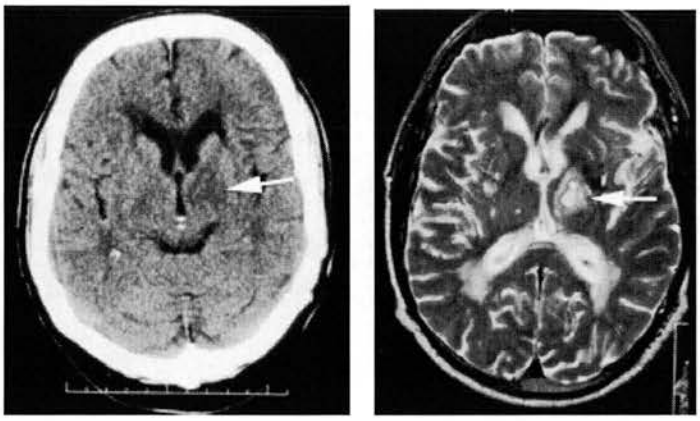


Figure 7. 77 year old woman with dysphasia, right homonymous hemianopia, resolved. Scanned 6 days after onset of symptoms. CT on left, gradient echo right.

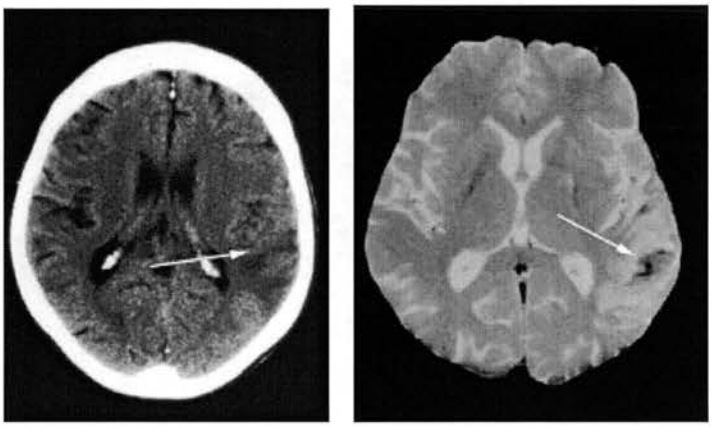


Figure 8. 52 year old woman with expressive dysphasia almost resolved. Scanned 28 days after onset of symptoms.

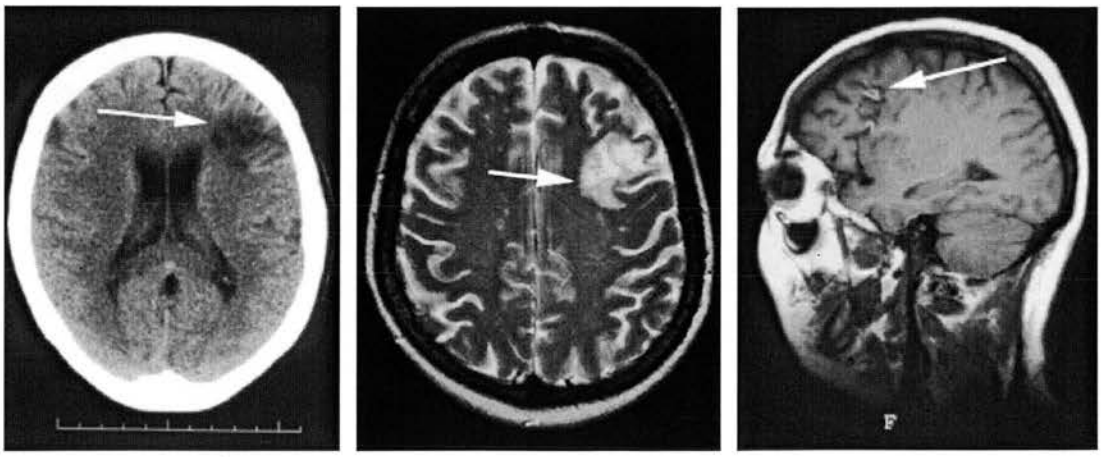


Figure 9. 88 year old woman with dysphasia and right inattention. Scanned at 5 days.

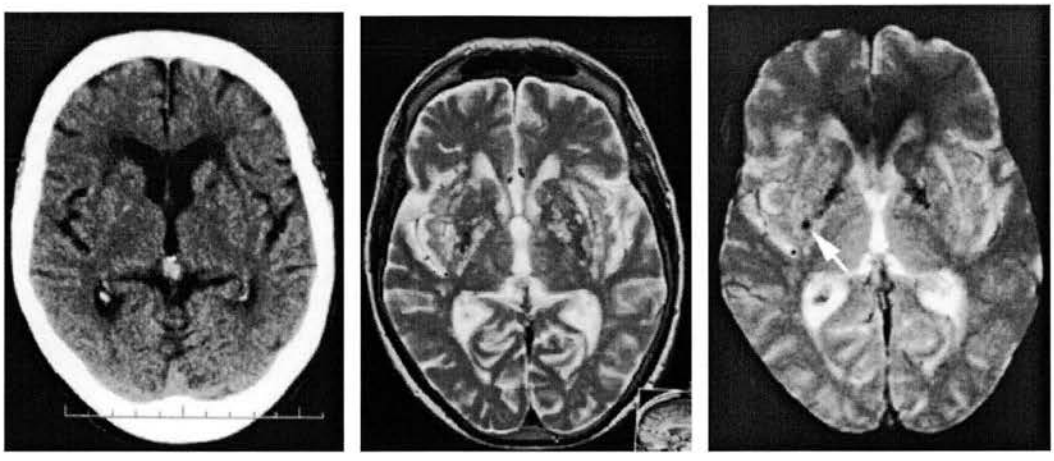


Figure 10. 82 year old woman with right hand weakness, mild weakness persists. Scanned 21 days after onset of symptoms.

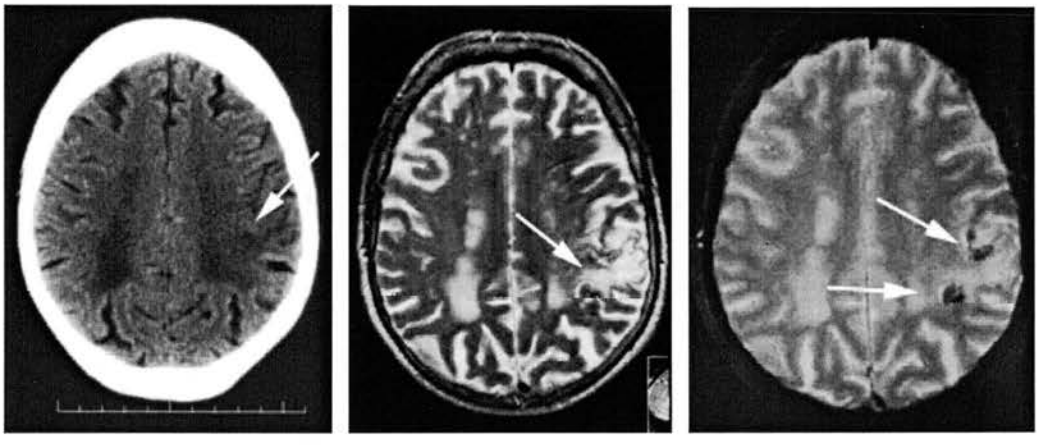


Figure 11. 72 year old woman with 4 transient episodes of right facial numbness, one associated with right hand parasthesia. Scanned at 28 days. CT on left, gradient echo right.

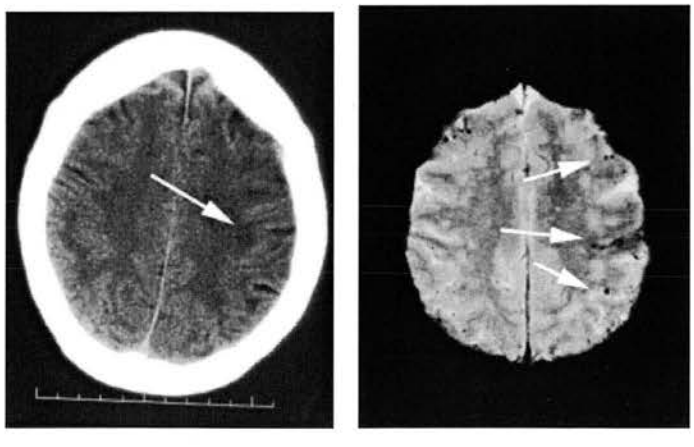


Figure 12. 72 year old man with ataxia and loss of balance to right, no residual abnormality. Scanned at 20 days. CT on left, gradient echo right.

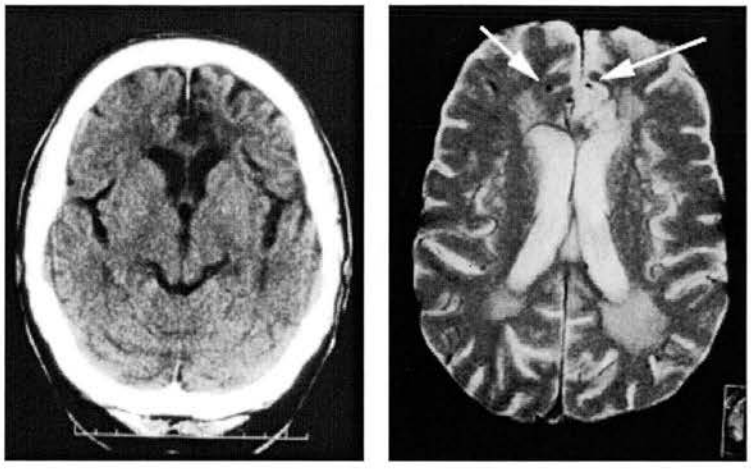


Figure 13. 70 year old man with expressive dysphasia, mild symptoms persist. Scanned at 19 days.

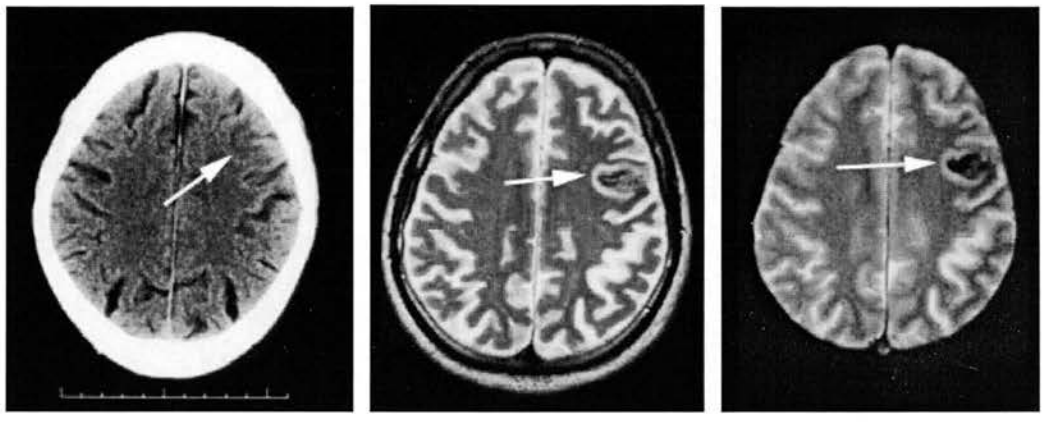


Figure 14. 70 year old woman with persistent mild left facial weakness. Scanned at 14 days.

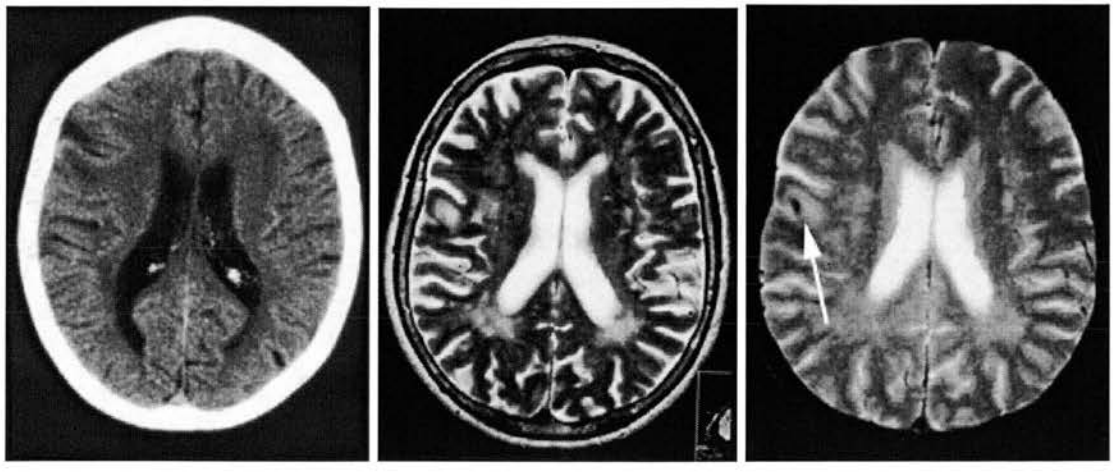


Figure 15. 70 year old woman with right homonymous hemianopia, no residual signs. Scanned at 28 days. CT on left, gradient echo on right.

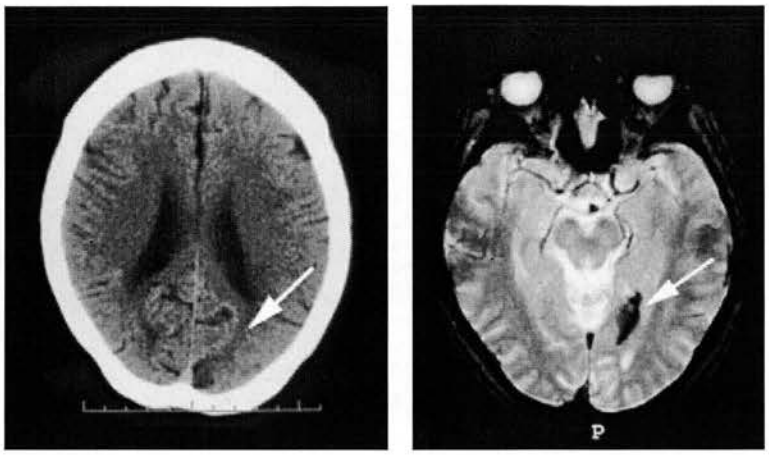


Figure 16. 72 year old woman with left homonymous field deficit. Scanned at 49 days.

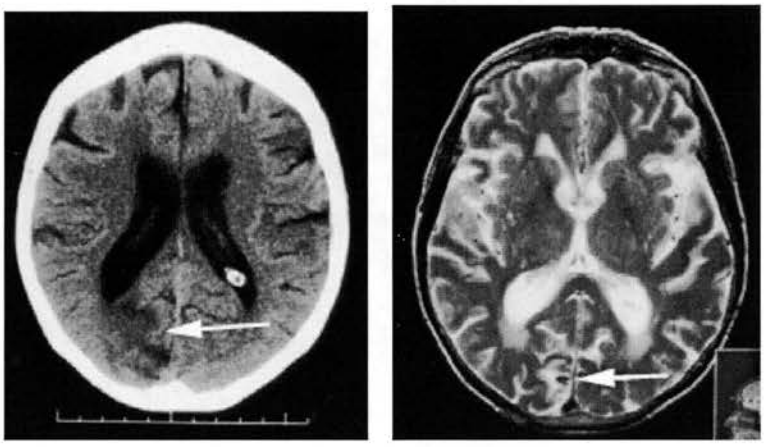


Figure 17. 62 year old man with right arm weakness and expressive dysphasia, mostly resolved. Scanned at 28 days. CT on left, gradient echo MRI on right.

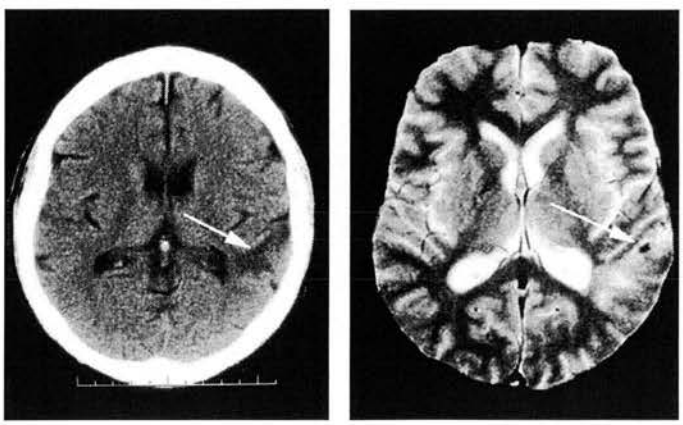
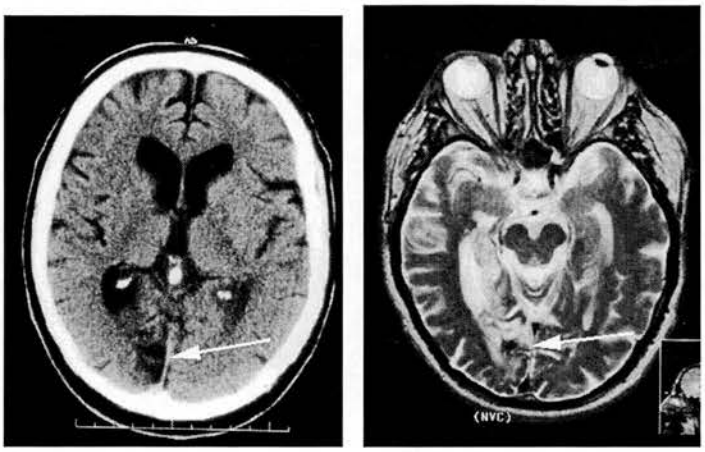


Figure 18. 72 year old man with left homonymous field deficit. Scanned at 56 days.



Effect of scan results on clinical decisions

A total of 223 clinical histories with accompanying relevant clinical details, were used. The nine stroke physicians (five Consultants and four Clinical Research Fellows) were each given a selection of histories ranging in number from 11 to 44 according to the physician's time constraints.

The physicians' diagnoses

Physicians were not asked to say definitively whether symptoms were due to stroke versus non-stroke, or infarct versus PICH. However, taking a physician certainty of greater than 90% as a definite diagnosis, the following diagnoses were made:

- With information on clinical features, examination and general investigations (i.e. no scan findings), physicians made the diagnosis of stroke (as opposed to non-stroke) in 153 cases (69%), of which 100% were felt to be due to infarction (with greater than 90% certainty).
- When also given the corresponding findings on CT, the diagnosis of stroke was made in 166 cases (74%), of which 153 (69%) were felt to be due to infarction, two (1%) to be PICH and 11 (5%) were equivocal (diagnosis could not be made with greater than 90% certainty).

- When also given the findings on MRI, the diagnosis of stroke was made in 169 cases (76%), of which 160 (72%) were felt to be due to infarction, eight (4%) to PICH and one (0.5%) was equivocal.

CT increased certainty of diagnosis of stroke versus non-stroke ($p = 0.006$), MRI less so ($p = 0.5$). However, MRI greatly increased certainty in the making of a diagnosis of PICH ($p < 0.001$).

Decisions changed following scan results

Management decisions were changed following knowledge of CT results in 39 cases overall (17.5%, 95% CI 12.5-22.5%). With MRI results, a further 28 (13%, 95% CI 8-17%) changes were made compared to decisions with CT findings (table 11).

Decisions changed regarding the use of an antithrombotic drug in 17 (7.6%) patients when histories were reviewed with CT results. Aspirin or another antiplatelet drug was started in seven patients (who were not previously on antithrombotic therapy), stopped in six, and continued in four when they had been stopped on history alone). Decisions regarding warfarin were changed in 12 (5.4%) patients (warfarin was started in nine patients, stopped in two patients, and continued in one patient following CT results when it had been stopped on history alone). If a warfarin decision was associated with an antiplatelet decision change, the latter was not counted separately. Decisions regarding endarterectomy were changed in 10 (4.5%) patients when CT results were available (eight patients were not referred, two patients were referred).

Decisions regarding using an antithrombotic agent were further altered in 14 (6.7%) patients with MRI results. Aspirin or another antiplatelet drug was started in one patient, and stopped in 13. Decisions regarding warfarin were changed in six (2.7%) patients (warfarin was stopped in three patients, all of whom had PICH or HTI, and started in three patients). Endarterectomy decisions were changed in eight (3.6%) patients (six patients were referred, two patients were not).

The pathway of clinical decisions in patients with scans showing haemorrhage

How decisions changed in patients with haemorrhage on their scans is documented in table 12.

- In the two patients in whom PICH was also seen on CT, antithrombotic drugs were continued in one patient and another antiplatelet drug was added to aspirin in the other on history alone. These were discontinued when haemorrhage was demonstrated on CT (and remained discontinued following MRI results).
- In the six patients in whom PICH was only identified on MRI, four had aspirin started, one continued aspirin, and in one patient warfarin was stopped on history alone. With knowledge of CT results, aspirin or another antiplatelet agent was commenced or continued in four patients, and the one patient on warfarin continued anticoagulation. Following MRI results all antithrombotic drugs or warfarin were stopped or not commenced.
- In the three patients with HTI documented on CT, aspirin was started or continued in two, and stopped in one on history alone. Following CT results, aspirin was not started in one patient, stopped in one, and was continued in one. Decisions were unchanged following MRI results
- In the twelve patients with HTI seen only on MRI, it seemed that describing the extent of HTI (as trivial or moderate, no patients had extensive HTI) had no bearing on management. Aspirin or another antiplatelet drug were commenced or continued in all 12 patients on history alone. With CT results, aspirin or another antiplatelet agent were commenced in ten patients, and warfarin commenced in two. With MRI results, aspirin or another antiplatelet drug was started in all 12, warfarin was not started in any patients.

Variability of scan reading and management decisions

The neuroradiologist interpreting scans read 20 scans twice with a suitable time period between readings. Diagnoses were identical in 17 (85%), and in no scans with haemorrhage was a different diagnosis reached. One stroke physician repeated ten decision forms, another repeated five. Decisions were consistent in 90% and 40%

respectively. Comparing means of how certain the different physicians were in their diagnosis, there was significant variation ($p = 0.009$).

Patient preference questionnaire

Questionnaires were available for 192 patients. Of these patients, 82 (43%) underwent CT first, and 110 (57%) underwent MRI first. 150 patients (78%) preferred CT, compared with 13 (7%) preferring MRI and 29 (15%) expressing no preference. All patients felt they would agree to a further CT scan if they had to, and 99% would agree to an MRI, although four patients added that it would be under duress. 21 patients commented on the friendliness and helpfulness of the staff. Other comments included: the MRI was noisy (11), claustrophobic (6), too long (5), and frightening (2). One patient liked the noise of the MRI scanner, one felt more secure in the MRI scanner and found it more relaxing than CT (they felt they would fall off the CT table).

5.4 Discussion

Blood-sensitive MRI sequences can identify ICH years after the event

In our late haemorrhage study, the blood-sensitive gradient-echo sequence (GRE) identified evidence of ICH on all scans (100%). The next most sensitive sequences were T1 and T2-weighted spin echo imaging, identifying ICH on 97% and 93% of scans respectively. PD and FLAIR sequences were much less effective at identifying ICH. These values compare favourably with the study investigating the persistence of evidence of ICH following traumatic head injury (90%), although GRE was not performed in that study[6]. Although the proportions of routine T1 and T2-weighted imaging on which haemorrhage could still be seen are high, they are not 100%, and our series was small. Gradient-echo imaging is not performed routinely, and thus there is the likelihood that a small proportion of patients (in our case series, 3%) with previous ICH will be missed if only routine structural imaging is performed.

Evidence of ICH was identified over eight years after the original event, remaining visible on GRE, T1 and T2-weighted imaging. Whether haemosiderin persists indefinitely is unclear. Also, the reason why haemorrhage disappears completely from a small proportion of images is unclear.

The late haemorrhage study demonstrates that in the vast majority of this population of patients with ICH, the evidence of ICH remained on certain sequences of MRI for as long after the original event as we were able to scan, which in this study was over eight years. This makes it an ideal imaging tool to detect late haemorrhage, so long as the correct sequences, i.e. gradient echo, are performed.

MRI is well tolerated

In the CT versus MRI study, we found that only a very small proportion of our study population (1.7%) were unable to undergo MRI, and that although the vast majority

preferred CT, they would undergo MRI again if necessary. One important feature that improves the acceptability of the procedure seems to be friendly and reassuring staff.

MRI identified more haemorrhage than CT

In our CT versus MRI study, MRI identified more haemorrhage than CT. MRI proved superior in the detection of both primary intracerebral haemorrhage (PICH) and haemorrhagic transformation (HTI). CT did not identify any cases of haemorrhage that were not also identified on MRI. We have no criteria against which to judge MRI, but assuming MRI to be the gold standard, the sensitivity of CT in the detection of PICH and HTI in this group of patients was 50% and 20% respectively.

How many minor strokes may have had haemorrhage in the general population?

The estimated number of patients being treated in the community in the UK is about 22000 per year. The use of aspirin has increased dramatically in the last decade[7,10] and stroke physicians are exhorted to consider warfarin in increasingly older populations of patients with atrial fibrillation[11,12]. The frequency of PICH in our study population was 3.5% and of HTI was 6.6%. From Stroke Association Survey estimates of patients in the community presenting with stroke symptoms, these would represent around 2200 patients per year in whom antithrombotic or anticoagulant treatment would be considered.

Timing of scanning in relation to sensitivity of CT

This group of patients, which represented a typical population presenting in the main, to a neurovascular clinic were scanned an average of three weeks after their stroke. A major delay to scanning was the time to presentation to the GP, as there was only a short delay once referred. This time delay definitely has a detrimental effect upon the sensitivity of CT in the detection of ICH[13,14]. In our study, CT missed 17/23 (74%) of all haemorrhage identified on MRI. The earliest time-point at which a PICH was missed on CT was 11 days (and because the scan was not performed any earlier, it is impossible to say precisely the earliest time-point at which the PICH would have been missed). The latest time PICH

was identified on CT was 14 days. These timings, both of presentation to scan and CT findings highlight an important point. The much-reduced sensitivity of CT for identifying haemorrhage more than 10 days after onset of stroke symptoms is such that its use to rule out the possibility of haemorrhage (as opposed to identifying a non-stroke lesion) must be must be questioned.

What is the true frequency of asymptomatic haemorrhage?

Follow-up scanning identified evidence of haemorrhage in 12/26 (46.2%) patients in the late haemorrhage study, which was presumed asymptomatic as further scanning had not been performed in the interim. Signs of old asymptomatic haemorrhage were also found on MRI in the CT versus MRI study but in far fewer patients (15, 6.6%). Although in patients with recent haemorrhage or haemorrhagic transformation in the CT versus MRI study, the proportion was slightly higher (8.9%), it was still far from the values of up to 68% given in previous studies looking for asymptomatic haemorrhage specifically[3,4,15,16] (see chapter 4). Differences in case-mix between studies, both in terms of age and clinical presentation may well account for much of this variation.

Do imaging results really matter?

It may be that patients with PICH found only on MRI would have come to no harm had their antithrombotic treatment not been stopped. Certainly, the outcome of patients with minor haemorrhagic stroke given antiplatelet drugs or warfarin is not known. However, the analysis of IST/CAST data on antithrombotic treatment following PICH (chapter 3) does include the possibility of harm. In our study, knowledge of scan results made a difference to clinical management in 17% of cases following CT results, and in a further 12% following MRI results. Whether the proportion of changes is large enough to alter scanning policy however, is debatable. Although clinicians prefer to have scans (certainty of diagnosis was increased), and patients prefer to have scans (personal observation), if access to imaging is relatively limited, figures such as found in our study may not prove convincing enough to justify a 'scan everyone' policy. The variability within and between

doctor's decisions in our study makes it impossible to say these figures are definitive, but do help to quantify the contribution of imaging to the overall management of the patient.

Should we be using MRI more?

To be sure that a patient presenting with stroke symptoms more than ten days after the event has not had a haemorrhagic stroke, an MRI is required. Access to MRI is very limited in the UK[11], and where accessible there may be waiting times of many weeks. If we were to wait for MRI before treating all patients presenting after ten days (assuming it was possible to get an MRI), this would create an unacceptable level of delay in commencement of secondary prevention treatment for the majority of patients. However, there is no doubt that in specific groups of patients, MRI provides more information than CT, and this information, as demonstrated in the CT versus MRI study patients with PICH, may alter clinical management. The next challenge will be to determine precisely who should be placed on the MRI waiting list (and whether they should be given aspirin whilst they are waiting). Certainly 'salvage' by MRI because it is too late to CT would rarely be a credible option. More realistically, patients should be encouraged to seek medical attention early after *any* stroke, and hospital clinics and imaging departments should offer responsive and rapid access to medical and CT assessment in line with current guidelines.

Table 1. Late haemorrhage study. Baseline characteristics

	Mean	Median	Range	Standard Deviation
Age (years)	66.5	69	42-87	10.9
Time from CT(months)	39.9	30.7	7.6-100.3	22.9
Infarct volume (cm^3)	23.9	18	1-80	22.9

Table 2. Late haemorrhage study. Distribution of haematomas on original CT

Site	Left	Right	Midline
Frontal lobe	1	4	
Basal ganglia	6	4	
Thalamus		2	
Temporal lobe	2		
Parietal lobe	2	2	
Occipital lobe	1	2	
Occipito-parietal lobe	1		
Brainstem/cerebellum		1	1

Table 3. Late haemorrhage study. Corresponding findings on different sequences at follow-up MRI

Scan finding	MRI sequence (%)				
	T1	Proton density	T2	FLAIR	Gradient echo
Lesion visible as haemorrhage	28 (97)	17 (59)	27 (93)	0	29 (100)
Lesion thought to be infarct	0	5 (17)	0	18 (62)	0
Uncertain	0	2 (7)	0	1 (3)	0
No residual lesion	1 (3)	5 (17)	0	9 (31)	0
Scan uninterpretable	0	0	2 (7)	1 (3)	0

Table 4. Secondary lesions on CT and secondary findings on follow-up MRI

CT findings		Secondary lesion finding at follow-up MRI				
Site of primary lesion (haematoma) on CT	Secondary lesions on CT	T1/FES T2	FSE PD	SE T2	FLAIR	GRE T2
R basal ganglia lacune	none	none	none	Haemorrhage L basal ganglia Infarct L cerebellum	Infarct L lacune	Haemorrhage spots L basal ganglia, pons, R thalamus
R frontal lobe	Infarct R occipital lobe	Old secondary lesion still visible	none	Haemorrhage L parietal lobe	none	Old secondary lesion still visible and haemorrhage (and haemorrhagic transformation) L parietal lobe x2
L basal ganglia	Infarct R centrum semiovale lacune	Old secondary lesion still visible	none	none	Infarct R centrum semiovale lacune	none
R basal ganglia	none	Haemorrhage superior cerebellum	Haemorrhage L thalamus	Haemorrhage: superior cerebellum R frontal lobe L thalamus	none	Haemorrhage black spots everywhere
L anterior temporal lobe	none	none	none	Infarct R frontal lobe	none	none
L temporal lobe	none	none	none	none	none	Haemorrhage black spots R frontal, L parietal
L basal ganglia	none	Infarct L temporal lobe	Infarct R centrum semiovale lacune	none	none	Haemorrhage R basal ganglia
R parietal lobe	Infarct L BG lacune	none	none	none	none	Old secondary lesion still visible
R basal ganglia	none	Infarct L parietal lobe, L centrum semiovale lacune	none	Haemorrhage L basal ganglia; Infarct old R parietal lobe	Infarct; lots of lacunes	none

CT findings		Secondary lesion finding at follow-up MRI				
Site of primary lesion (haematoma) on CT	Secondary lesions on CT	T1/FES T2	FSE PD	SE T2	FLAIR	GRE T2
Mid pontine	none	Infarct R thalamus lacune L centrum semiovale lacune	none	Scan unreadable	none	Infarct L basal ganglia lacune
L parieto-occipital lobe	none	none	none; Infarct – R centrum semiovale lacune	none	none	Haemorrhage - L thalamus dot
R thalamus	none	Infarct R centrum semiovale lacune, R thalamus	none	Scan unreadable	none	Haemorrhage black dots L thalamus, lentiform nucleus
L basal ganglia	Infarct L middle cerebral artery, R cerebellum	Old secondary lesion still visible	none	none	Infarct L parietal borderzone	
R frontal lobe and L occipital lobe	Infarct R occipital lobe	L cerebellum	none	Infarct L cerebellum	Infarct L parietal cortex	Haemorrhage: R occipital lobe (not infarct as on CT); L frontal R parietal dots
R cerebellum and R frontal lobe	none	none	none	Haemorrhage R temporal lobe Infarct R centrum semiovale lacune	Infarct R centrum semiovale lacune	Haemorrhage R postero-temporal lobe. Infarct R centrum semiovale lacune Haemorrhage black dots everywhere
L basal ganglia	none	none	none	Infarct L parieto-occipital lobe	Infarct L parieto-occipital lobe	Infarct L parieto-occipital lobe
R basal ganglia	none	Infarct none; L basal ganglia lacune	none	none	none	none
L basal ganglia	none	none	none	none	none	Haemorrhage R basal ganglia
R occipital lobe and L parietal lobe	none	Infarct none; R cerebellum	none; ?Haemorrhage: tiny L basal ganglia	none	Infarct R cerebellum lacune	Haemorrhage black spots everywhere

CT findings		Secondary lesion finding at follow-up MRI				
Site of primary lesion (haematoma) on CT	Secondary lesions on CT	T1/FES T2	FSE PD	SE T2	FLAIR	GRE T2
L parietal lobe	Infarct R fronto-parietal and R occipital lobe	Old secondary lesion still visible and infarct L cerebellum	Old secondary lesion still visible	Haemorrhage R frontal (not infarct as on CT); 2	none	Old secondary lesion still visible and haemorrhage:black spots everywhere

Table 5. Late haemorrhage study. Other findings on follow-up

	Number	Percentage (%)
Atrophy	20	69
Enlarged perivascular spaces (T2)	16	55
Small vessel disease (FLAIR)	18	62
Haemorrhage spots (GRE)	8	28
Basal ganglia spots (GRE)	8	28

Table 6. CT versus MRI study. Baseline characteristics

	Age (years)	Time from onset of symptoms to scanning (days)	Canadian Neurological score at examination
Mean	67.5	21.7	9.5
Median	68.0	20	9.5
Range	35 – 89	2 – 112	5.5 – 10
Standard Deviation	9.9	15.3	1.0

Table 7. CT versus MRI study. Distribution of stroke subtype according to the OCSP classification

Subtype	Number	Percent %
PACS	101	44.2
LACS	73	32.0
POCS	36	15.8
Undefined	24	9.0
Total	228	100

Table 8. CT versus MRI study. Agreements, disagreements and corresponding findings on CT and MRI

	CT Findings*										Total
MRI findings*		RI	HTI	RH	OLPI	OLPH	MPVL	CA	Normal	Tumour	
	RI	86	0	0	8	0	7	8	12	1	122
	HTI	10	2	1	1	0	1	0	0	0	15
	RH	5	0	2	1	0	0	0	0	0	8
	OLPI	2	0	0	4	0	2	0	1	0	9
	OLPH	2	0	0	0	0	0	1	2	0	5
	MPVL	9	0	0	0	0	3	9	8	0	29
	CA	1	0	0	1	0	0	6	1	0	9
	Normal	4	0	0	2	0	0	3	19	0	28
	Other	0	0	0	0	0	0	0	0	3	3
Total		119	2	3	17	0	13	27	43	4**	228

RI – recent infarct, HTI – haemorrhagic transformation, RH – recent haemorrhage, OLPI, old lesion probable infarct, OLPH – old lesion probable haemorrhage, MPVL – multiple periventricular lucencies, CA – cortical atrophy.

*Because of overlapping reporting of OLPI, OLPH and incidental meningioma with other more principal diagnoses, the only scans documented with this finding here are those where these were not associated with recent infarct, recent haemorrhage or HTI

**CT identified a further meningioma in a patient with a recent infarct thus giving a total of five meningiomas identified

Table 9. CT versus MRI study. Scan findings in patients with haemorrhagic changes and timing of scanning in relation to onset of symptoms

Code	Type and extent of Haemorrhage	Time from scan (days)	Clinical history
3439	PICH	11	R hemiparesis and dysphasia, mild weakness persists
4336	PICH	13	Mild R hemiparesis including face, residual mild R facial weakness
4417	PICH	14	R arm and hand numbness lasted 2 days. Persistent reduced fine finger movement
4119	PICH	17	Ataxia, blurring of R field of vision, no residual neurological signs
4636	PICH	21	Right arm and leg weakness and facial numbness, residual reduced fine finger movements.
3995	PICH	28	Headache, scarred vision, persistent L inferior quadrantonopia
4548	HTI medium	6	Receptive and expressive dysphasia, R homonymous lower quadrantonopia unresolved
3996	HTI medium	19	Expressive dysphasia, mostly improved
3043	HTI medium	20	Vomited, ataxia, falling to right, no residual neurological abnormality
3766	HTI medium	28	Probable R homonymous hemianopia no residual signs, possibly migraine
4042	HTI medium	28	4 transient episodes of right facial numbness, one associated with right hand parasthesia
3654	HTI medium	56	20 minute episode of dysarthria followed by persistent L homonymous field deficit
4135	HTI trivial	5	R lower homonymous field defect, dysphasia, R inattention
4414	HTI trivial	14	Dysarthria, noted L facial weakness, still persists (mild)
4137	HTI trivial	21	Transient L hand weakness then following day R hand weakness. Residual decreased sensation R hand
3693	HTI trivial	28	Expressive dysphasia, almost back to normal. R arm weakness when tired for last year
3824	HTI trivial	28	R arm weakness and expressive dysphasia, mostly resolved
824	HTI trivial	49	L homonymous field defect 3 days following thrombolysis for MI
4067	PICH also seen on CT	4	Word finding difficulty and difficulty with comprehension for 1 week
4403	PICH also seen on CT	14	L hemiparesis (mild) and pins and needles. Residual mild facial defect
4113	HTI on MRI thought PICH on CT	9	Left hand weakness, symptoms improving but still present
4220	HTI also seen on CT	17	Dysarthria, L arm sensory disturbance, L leg weakness, symptoms (mild) persist in leg
4581	HTI also seen on on CT	18	Headache followed by confusion, dressing apraxia, residual R homonymous hemianopia

PICH – primary intracerebral haemorrhage
HTI – haemorrhagic transformation

Table 10. Doctors decisions. History alone then history with CT results

		History with CT results								
	Decisions	Start aspirin	Start aspirin and another antiplatelet agent	Stop aspirin	Continue aspirin	Start another antiplatelet agent	Continue aspirin and start another antiplatelet agent	Not applicable	Scan required for another diagnosis	Total
History alone	Start aspirin	44	1	0	3	3	0	3	0	54
	Start aspirin and another antiplatelet agent	0	0	0	0	0	0	0	0	0
	Stop aspirin	1	0	3★	3	0	1	0	0	8
	Continue aspirin	8	0	7*	72	5	18	1**	1	112
	Start another antiplatelet agent	2	0	0	2	8	0	1†	0	13
	Continue aspirin and start another antiplatelet agent	1	0	2✠	2	11	5	0	0	21
	Not applicable	6	0	0	1	0	0	7	1	15
	Scan required for another diagnosis	0	0	0	0	0	0	0	0	0
	Total	62	1	12	83	27	24	12	2	223

Anticoagulation (AC) commenced in *5 patients, **1, †1, ✠1, ★1
Overall: following CT, anticoagulation commenced in 9 patients, not started in 1 patient when started following history only, and continued in 1. (in 9/11, changes also made in aspirin decisions)

Table 11. Doctors decisions. With CT results, then with MRI results

		History with MRI results								
	Decisions	Start aspirin	Start aspirin and another antiplatelet agent	Stop aspirin	Continue aspirin	Start another antiplatelet agent	Continue aspirin and start another antiplatelet agent	Not applicable	Scan required for another diagnosis	Total
History with CT results	Start aspirin	44	0	0	4	3	2	9	0	62
	Start aspirin and another antiplatelet agent	1	0	0	0	0	0	0	0	1
	Stop aspirin	0	0	10	1*	0	0	1	0	12
	Continue aspirin	2	0	2**	69	6	2	2	0	86
	Start another antiplatelet agent	2	0	1**	2	8	14	0	0	27
	Continue aspirin and start another antiplatelet agent	0	1	0	9	2	12	0	0	24
	Not applicable	1	0	2*	0	1	0	8*	0	12
	Scan required for another diagnosis	0	0	0	0	0	0	0	2	2
	Total	50	1	15	85	20	30	20	2	223

Anticoagulation stopped in: * 3 patients
Anticoagulation started in ** 2 patients

Table 12. Decisions taken regarding patients with haemorrhage, with and without scan results

Patient code	Extent of haemorrhage	Time from scan (days)	Decisions made regarding antithrombotic therapy			Decisions made regarding anticoagulant therapy		
			History alone	With CT results	With MRI results	History alone	With CT results	With MRI results
3439	PICH	11	Start aspirin	Start aspirin	Not relevant	Not relevant	Not relevant	Not relevant
4336	PICH	13	Not relevant	Not relevant	Not relevant	Stop warfarin	Continue warfarin	Stop warfarin
4417	PICH	14	Start aspirin	Start aspirin	Not relevant	Not relevant	Not relevant	Not relevant
4119	PICH	17	Start aspirin	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant
4636	PICH	21	Start aspirin	Start aspirin	Not relevant	Not relevant	Not relevant	Not relevant
3995	PICH	28	Continue aspirin	Continue aspirin & start another antiplatelet agent	Stop aspirin	Not relevant	Not relevant	Not relevant
4548	HT (moderate)	6	Continue aspirin	Continue aspirin	Continue aspirin	Not relevant	Not relevant	Not relevant
3996	HT (moderate)	19	Continue aspirin	Continue aspirin	Continue aspirin	Not relevant	Not relevant	Not relevant
3043	HT (moderate)	20	Continue aspirin	Continue aspirin	Continue aspirin	Not relevant	Not relevant	Not relevant
3766	HT (moderate)	28	Continue aspirin	Continue aspirin & start another antiplatelet agent	Continue aspirin	Not relevant	Not relevant	Not relevant
4042	HT (moderate)	28	Continue aspirin & start another antiplatelet agent	Continue aspirin	Continue aspirin	Not relevant	Not relevant	Not relevant
3654	HT (moderate)	56	Continue aspirin	Continue aspirin	Continue aspirin	Not relevant	Not relevant	Not relevant

Patient code	Extent of haemorrhage	Time from scan (days)	Decisions made regarding antithrombotic therapy			Decisions made regarding anticoagulant therapy		
			History alone	With CT results	With MRI results	History alone	With CT results	With MRI results
4135	HT trivial	5	Start another antiplatelet agent	Start another antiplatelet agent	Start aspirin	Not relevant	Not relevant	Not relevant
4414	HT trivial	14	Start aspirin	Start aspirin	Start aspirin	Not relevant	Not relevant	Not relevant
4137	HT trivial	21	Continue aspirin	Stop aspirin	Continue aspirin	Not relevant	Start warfarin	Not relevant
3824	HT trivial	28	Start aspirin	Start aspirin	Start aspirin	Not relevant	Not relevant	Not relevant
3693	HT trivial	28	Continue aspirin	Continue aspirin	Continue aspirin & start another antiplatelet agent	Not relevant	Not relevant	Not relevant
824	HT trivial	49	Start another antiplatelet agent	Not relevant	Start another antiplatelet agent	Not relevant	Start warfarin	Not relevant
4067	Seen on CT (HTI)	4	Start aspirin	Not relevant	Stop aspirin	Not relevant	Not relevant	Not relevant
4113	Seen on CT (PICH)	9	Continue aspirin & start another antiplatelet agent	Stop aspirin	Stop aspirin	Not relevant	Not relevant	Not relevant
4403	Seen on CT (PICH)	14	Continue aspirin	Stop aspirin	Stop aspirin	Not relevant	Not relevant	Not relevant
4220	Seen on CT (HTI)	17	Stop aspirin	Stop aspirin	Stop aspirin	Not relevant	Not relevant	Not relevant
4581	Seen on CT (HTI)	18	Continue aspirin	Continue aspirin	Continue aspirin	Not relevant	Not relevant	Not relevant

1. Hung TP,.Lee KY. Small intracerebral haemorrhage: a study of clinical manifestations and CT findings on 31 cases. Annals of the Academy of Medicine, Singapore 1985;14:22-31.

2. Dennis MS, Bamford JM, Molyneux AJ, Warlow CP. Rapid resolution of signs of primary intracerebral haemorrhage in computed tomograms of the brain. BMJ 1987;295:379-81.

3. Kwa VIH, Franke CL, Verbeeten Jr B, Stam J. Silent intracerebral microhaemorrhages in patients with ischaemic stroke. Ann Neurol 1998;44:372-7.

4. Greenberg SM, Finklestein SP, Schaefer PW. Petechial hemorrhages accompanying lobar hemorrhage: detection by gradient-echo MRI. Neurology 1996;46:1751-4.

5. Darrow VC, Alvord EC, Jr., Mack LA, Hodson WA. Histologic evolution of the reactions to hemorrhage in the premature human infant's brain. A combined ultrasound and autopsy study and a comparison with the reaction in adults. Am.J.Pathol. 1988;130:44-58.

6. Wardlaw JM,.Statham PF. How often is haemosiderin not visible on routine MRI following traumatic intracerebral haemorrhage? Neuroradiology 2000;42:81-4.

7. Ebrahim, S. and Redfern, J. Stroke Care - a matter of chance. A national survey of stroke services. 1999. London, The Stroke Association.

8. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991;337:1521-6.

9. Cote R, Hachinski VC, Shurvell BL, Norris JW, Wolfson C. The Canadian Neurological Scale: a preliminary study in acute stroke. Stroke 1986;17:731-7.

10. Lindley, R., Amayo, E., Marshall, J., Sandercock, P. A. G., Dennis, M. S., and Warlow, C. P. Acute Stroke Treatment in UK hospitals: the Stroke Association survey of consultant opinion. Journal Royal College of Physicians of London 29, 479-484. 1995.

11. Wensley S, Keir S, Caine S, MacMahon M. Additional risk factors in atrial fibrillation patients not receiving warfarin. Age & Ageing 1999;28:355-7.

12. Mead GE, Wardlaw JM, Lewis SC, McDowall M, Dennis MS. The influence of randomized trials on the use of anticoagulants for atrial fibrillation. Age Ageing 1999;28:441-6.

13. Mayer TE, Schulte-Altedorneburg G, Droste DW, Bruckmann H. Serial CT and MRI of ischaemic cerebral infarcts: Frequency and clinical impact of haemorrhagic transformation. Neuroradiology 2000;42:233-9.

14. Steinbrich W, Gross-Fengels W, Krestin GP, Heindel Schreier WG. MRI examinations of intracranial hmatomas. an analysis of its sensitivity evolution and source of bleeding. Rofo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin 1990;152:534-43.

15. Tanaka T, Sakai T, Uemura K, Teramura A, Fujishima I, Yamamoto T. Magnetic resonance imaging in the acute stage of cerebrovascular disease - Clinical comparison with computed tomography. Neurologia Medico-Chirurgica 1988;28:(pp 974-80).

16. Kinoshita T, Okudera T, Tamura H, Ogawa T, Hatazawa J. Assessment of lacunar hemorrhage associated with hypertensive stroke by echo-planar gradient-echo T2*-weighted MRI. Stroke 2000;31:1646-50.

6 The Sensitivity Of CT And Conventional MRI Techniques In Making A Positive Diagnosis Of Ischaemic Stroke

6.1 Introduction

Making a positive diagnosis of stroke is important when considering hyperacute stroke treatment

Chapters 2, 3 and 4 addressed the importance of accurately distinguishing haemorrhagic from ischaemic stroke. Having excluded haemorrhage and non-vascular causes of stroke, making a positive diagnosis of infarction on neuroimaging is currently of less importance; aspirin would be started on the basis of an appropriate history and examination and a scan with no obvious abnormality. However, the introduction of thrombolysis for hyperacute stroke may mean that current practice will change. The benefits of thrombolysis may be much greater than for antiplatelet agents, but unfortunately, so are the risks[1]. Although the precise time window within which thrombolysis can be given to good effect is uncertain, it is relatively short, probably only a matter of hours. Consequently clinicians do not have the luxury of time to help them decide whether to give the drug. Experience from the USA, where rtPA (recombinant tissue plasminogen activator, a thrombolytic agent) has been licensed for some time shows that only a small fraction of patients arriving in hospital and are eligible for the drug are receiving it[2,3]. Part of the reason for this may well be the reluctance of physicians to expose their patients to the (potentially fatal) risk of thrombolysis if they are not certain that the patient is definitely having a stroke (as opposed to a severe TIA for instance). Making a positive identification of ischaemia would increase clinical certainty.

A systematic review of CT and MRI in the positive identification of ischaemic stroke

It is important therefore, to have a grasp of the relative merits of both CT and MRI in making an accurate diagnosis. For example, involvement of greater than one third of the territory of the middle cerebral artery has been suggested as a contraindication to

thrombolysis[4]. Is this a realistic criterion? Although changes associated with ischaemic stroke can be demonstrated on conventional CT very soon after onset of stroke symptoms, they can be subtle[5-7]. It is important to know whether these changes can be identified consistently by multiple observers. Also, objective methodological criteria are again important. Sensitivities derived from a retrospective study of high quality scans interpreted alongside other imaging are likely to give a different result from one in which a more clinically realistic scenario was attempted. Bearing these issues in mind, a systematic review of the sensitivity of CT and conventional MRI in the positive identification of ischaemic stroke, and the inter-observer reliability of image interpretation was performed.

6.2 Methods

Search strategy

An electronic search of all published records of sensitivity of CT, MRI or both in the identification of ischaemic stroke was performed, using the electronic databases MEDLINE, from 1966 and EMBASE, from 1980 to the present day. In view of the overlap in studies and to ensure maximum capture of references, the same search strategy was used as for the identification of studies of the sensitivity of scanning in ICH (chapter 4 and appendix III). Reference lists were also consulted in articles found.

Data extraction

Data were extracted on:

- The number of patients in the study;
- Its primary purpose;
- The nature of the stroke population (e.g. unselected strokes, or a specific clinical type);
- Whether patients were assessed by a stroke physician or neurologist;
- Whether imaging was read blinded to clinical history or other imaging;
- The criteria upon which the final diagnosis of stroke was made;
- Timing of scanning in relation to stroke symptoms; and
- Values for scanning sensitivity in the positive identification of ischaemic stroke.

Only sensitivity data from studies in which the patient population had been seen by a stroke physician (as opposed to a potentially retrospective collection of patients in whom the differential diagnosis included stroke) were used. In studies concerning MRI, any details on the feasibility of scanning in the acute setting (e.g. numbers of patients it was not possible to scan or uninterpretable scans) were also noted. Case reports and descriptive studies of only one specific sign of ischaemia (e.g. hyperdense middle cerebral artery sign) were excluded.

Also, from the main search, studies were identified concerning either the accuracy of observer interpretation of lesions or the inter-observer reliability of interpretation of images.

Data analysis

Data were entered into an Access database and analysed with descriptive statistics.

6.3 Results

6.3.1 Studies of CT alone in the identification of ischaemia

Included studies

Thirty-one studies (7393 patients) concerning CT and stroke were identified, 15 of which (4604 patients) documented patient populations that had been seen by a neurologist or a physician with an interest in stroke, and documented values from which sensitivity for CT in the positive identification of ischaemic stroke could be calculated (table 1). These studies are discussed further below (see table 2 for the excluded studies).

Study populations

In the 15 included studies, the population group under investigation varied; five studies (895 patients) specifically excluded haemorrhage[8-12]; three studies (853 patients)

investigated unselected stroke populations[13-15]; three studies (145 patients) included infarcts of the middle cerebral artery territory only[16-18]; two studies (156 patients) included thrombolysis patients only[19;20]; one study included patients with various neurological diseases (1191 patients, 386 of which had stroke symptoms)[21], and one study included patients with mild stroke symptoms only[22]. These marked differences in case-mix make it difficult to draw any generalisable conclusions.

General methodological details

Nine studies (3571 patients, 60% of studies) recruited patients prospectively[8;10;12;13;15-17;21;22]. Only six studies (3001 patients, 40% of studies) were blinded to clinical history[9;11] or clinical history and other imaging[16;18;19;22]. The objective criteria for the final diagnosis of ischaemic stroke was: clinical progress and diagnosis at discharge in 11 studies (3334 patients, 73% of studies)[9-15;17;18;20;21], follow-up scan in two studies (83 patients, 13% of studies)[19;23], and undefined in three studies (1233 patients, 20% of studies)[8;16;22].

Values for sensitivity and specificity

No study examined a population from which an estimate of specificity could be made. The sensitivity of CT in the demonstration of an appropriate ischaemic lesion varied from 0.4 to 0.95. With the exception of one study in which a proportion of images were read by two neurologists[22], all images in included studies were read by radiologists or neuroradiologists. In an attempt to identify factors other than case-mix that had an effect upon sensitivity, studies were grouped according to timing of scanning, and whether studies were retrospective or prospective. As ischaemic lesions become more obvious with time[24], it was assumed that if timing of scanning in relation to symptoms was the only major feature in determining sensitivity, then the lowest values would be for those studies performing scanning at the earliest time points. This was not found to be the case; in fact, some of the highest values for sensitivity were recorded from studies in which scans were performed within 6 hours (table 3). Grouping studies by whether images were read prospectively rather than retrospectively made no difference, the ranges for sensitivity of positive identification being 0.4-0.95 and 0.53-0.81 respectively.

Inter-observer agreement in CT scan interpretation

Twelve studies documented the proportions of observer agreement of interpretation of CT scans, or the inter-observer reliability of interpretation of scans using kappa values. The kappa statistic[25] is a measure of agreement between two observers beyond that expected from chance alone, where: k = 0 indicates agreement no better than chance, k = 1 perfect agreement, k = 0 - 0.2 poor agreement, k = 0.21 – 0.4 fair agreement, k = 0.41 – 0.6 moderate agreement, k = 0.61 – 0.8 good agreement, k = 0.81 – 1 excellent agreement.

None of the seven studies that documented kappa values (994 scans)[4;26-31] were designed to imitate the reading of scans in a true clinical situation. All included selections of retrospectively collected scans of patients with acute stroke (including scans from four thrombolysis trials) that were presented to different observers. They were asked to identify the presence of varying indicators of ischaemia, and kappa values were calculated for level of agreement (table 4). With the exception of the identification of haemorrhagic transformation, there was no sign of ischaemia that could be identified by all observers with better than moderate agreement.

The six studies (948 scans) that documented observer agreement as either proportions in agreement or percentage accuracy, tended to be the closer to real clinical situations[23;32-36]. Two studies documenting accuracy of interpretation of scans by emergency physicians noted 87 to 98% accuracy for all pathological lesions[32;33]. Values fell to 67% however, when emergency physicians were asked to identify lesions pertinent to the interpretation of ischaemia and haemorrhage only[35]. In this study, neurologists and radiologists interpreted ischaemia and haemorrhage on scans with greater accuracy (83%). In a study where one neuroradiologist (blinded to clinical history other than 'stroke' and all other imaging) assessed CT scans performed within six hours of stroke for parenchymal hypodensity and brain swelling, the sensitivity of interpretation was 82%[23]. However, in another study investigating agreement for whether there was greater than a third involvement of the middle cerebral artery territory (a scan criterion put forward as a contraindication to thrombolysis[37]), there was still only 64% agreement between neuroradiologists (table 5).

6.3.2 Studies of conventional MRI alone in the identification of ischaemia

Included studies

Eighteen studies (1638 patients) were identified concerning MRI alone in stroke (table 6); 15 (1560 patients) included patients assessed at some stage by a neurologist or stroke physician. Only four studies of three quite different groups of patients reported values for sensitivity. Two studies (64 patients) that scanned patients within the initial two days after stroke found sensitivities of 84%[38] and 88%[39] compared with follow-up MRI. One study (53 patients) found a sensitivity 65% for FLAIR MRI in patients scanned within 6 hours of their stroke compared with follow-up scan[40]. One study of 79 patients with clinical transient ischaemic attacks found a sensitivity of 35% for clinically compatible lesions[41]. In only one of the four studies, was imaging read blinded to clinical history[38]. As with CT, the differences in case-mix, timing of scanning and small numbers make these results of interest but difficult to generalise.

Excluded studies

In the remaining (excluded) studies, the primary purposes were: descriptions of clinicotopography or specific MRI characteristics (eight studies, 990 patients)[42-49]; explorations around the use of contrast agent or imaging parameters (five studies, 167 patients)[51-54]; and one study (seven patients) highlighting the important issue of negative MRI scans in clinically definite stroke[55].

6.3.3 Studies of both CT and MRI in the identification of ischaemia – existing data

Included studies

Twenty-eight studies (1650 patients) comparing CT and MRI directly in stroke were identified, of which 18 studies (808 patients) included patients who had been assessed

by a neurologist or stroke physician. 12 studies (609 patients) documented the number of positive findings on scans performed and are detailed below (table 8). See table 9 for details of the remaining studies.

Study populations

As previously, the patient groups under investigation differed (some studies including more than one patient group), ranging from: transient ischaemic attack (two studies, 41 patients)[56;57]; lacunar stroke (five studies, 166 patients)[56;58-61], cerebellar stroke (one study 14 patients)[62]; lateral medullary syndrome (one study, 6 patients)[63]; and unselected stroke (four studies, 356 patients) [64-67]. Again, studies were uniformly small.

General methodological details

Nine studies (75% of studies) collected data prospectively[56-58;60;61;64-67], six studies (50%) blinded readers of scans either to clinical history[56;57;60;65;67] or other imaging[64]. In only one study (0.8%), was the order in which CT or MRI were performed varied (although not randomised)[67]; two studies performed both scans on the same day but did not document the order in which they were done[57;59]; in five studies, CT was always performed before MRI[56;60;64-66]. The extent of the difference in times varied; in one study where all patients were scanned within 24 hours, CT was performed a mean of four hours earlier[65]. In another comparing strokes within the first three weeks, CT was performed a median of four days earlier[56]. In three studies the order of scanning was not defined[58;61;63].

Sensitivities of CT and MRI in the positive identification of stroke

In the two studies (82 patients) that included patients with transient ischaemic attack, MRI was markedly better at demonstrating ischaemic lesions in one study (21% on CT compared with 68% on MRI[56]), but less obviously better in the other (MRI demonstrated lesions not seen on CT in 14%, but CT demonstrated lesions not seen on MRI in 9%[57]).

In all four studies (356 patients) of unselected stroke patients, the proportions of scans that demonstrated ischaemic lesions ranged from 43 to 68% for CT, and 51 to 98% for MRI[64-67] (table 10). Only one study tested the difference between the two scan findings statistically and found no significant difference[67]. In the study where difference in positive identification was most marked, MRI had been performed up to a week after CT[66]. One study documented the results of two observers interpreting CT and MRI in stroke and found considerable differences between their interpretation of images (positive findings on CT ranged from 48-68%, and for MRI from 77-87%).

In all four studies of lacunar strokes, MRI demonstrated more clinically compatible lesions (table 11). The proportion of ischaemic lesions identified on scans ranged from 17 to 50% for CT and 78 to 94% for MRI[58-61]. In one study MRI scans were performed one to three days after CT[60]; in the rest, the order of scanning was not defined.

In the two remaining studies, MRI was consistently superior in the positive identification of ischaemic stroke, both in the cerebellum (100%, 14/14 compared with 43%, 6/14 for CT[62]), and in lateral medullary syndrome (83%, 5/6 compared with 33%, 2/6 for CT[63]). Both studies were extremely small and retrospective.

6.3.4 The CT versus MRI study - new data on the positive identification of ischaemia

Recent infarction

Our prospective case study comparing CT and MRI in stroke is a major new study. It is the largest to date (228 patients) and the only to scan all patients with both CT and MRI on the same day, varying the order of scanning. In this section new data on the ability of CT and conventional MRI to identify relevant recent infarction are presented. 'Relevant' is defined as a lesion in keeping with the timing and site of patient symptoms. See section 5.3 for methods, baseline characteristics and overall findings.

CT scanning identified a relevant recent infarction in 119 (52.2%, 95% CI 46.2 to 59.5%). MRI agreed in 86/119 (72.2%) of cases. In the patients where MRI did not agree with CT diagnosis, the findings on MRI were: HTI in 10 (8.4%), recent

haemorrhage in 5 (4.2%), old lesion probable infarct in 2 (1.7%), old lesion probable haemorrhage in 2 (1.7%), multiple periventricular lucencies with or without cortical atrophy in 10 (8.4%), negative scan in 4 (3.4%) (table 12).

MRI identified a relevant recent infarction in 122 (53.5%, 95% CI 47.0 to 60.0%) patients. CT agreed in 86/122 (70.5%) of cases. In the patients where CT did not agree with MRI diagnosis, findings on CT were: HTI in 1 (0.8%), old lesion probable infarct in 8 (6.6%), multiple periventricular lucencies with or without cortical atrophy in 14 (11.5%), meningioma incidental to symptoms in 1 (0.8%), negative scan in 12 (9.8%) (table 13).

Since we were investigating the ability of MRI to demonstrate ischaemic stroke as well as CT, MRI was not taken to be the gold standard against which we could make an estimate of sensitivity.

6.4 Discussion

Values for the sensitivity of CT vary widely

Studies documenting the sensitivity of CT in the identification of ischaemic stroke demonstrate that high levels of sensitivity can be achieved, but not consistently. The range of sensitivities were wide and confounded by the variety of stroke populations investigated, as well as timing of scanning in relation to onset of stroke symptoms, and level of experience of person interpreting the images. For instance, grouping studies according to timing of scanning (table 3) did not reveal that scan interpretation was necessarily less accurate in the hyperacute stage. Neuroradiologists were generally more sensitive in their interpretation of CT changes than emergency physicians[35]. However, the more impressive results associated with (highly trained) neuroradiologists were from retrospective studies. Neuroradiologists may not always be available, especially within six hours, and hence it may not be possible to reproduce these results in real-life. A good example of how different those results could be is the practice audit by general physicians in a Canadian hospital of the sensitivity of CT scanning in demonstrating a diagnostic lesion at 24 hours, and where it was found to be only 23%[68]. Another factor confounding a definitive estimate of the sensitivity of CT is the continuously evolving technology, rendering studies potentially obsolete almost as soon as they are published.

Inter-observer reliability is important

Since CT scanners became available for clinical use in the mid-1970s, with the increasing sophistication of scanning technology, the complexity of information we can derive and the quality standards we demand have also increased. When CT was first introduced, as was the case with ICH, early studies were content to merely describe clinicotopographical findings[69;70]. In this era of thrombolysis however, it may be necessary accurately (and reliably) to demonstrate the earliest changes of an ischaemic infarct. As changes become increasingly subtle, the inter-observer reliability with which such changes can be seen becomes critically important. If a sign on CT cannot be distinguished reliably by multiple observers with varying levels of ability, it is of no use as a marker by which to alter clinical decisions (such as whether or not to give thrombolysis). So far, it seems that signs of early ischaemia on CT are too subtle for multiple observers to consistently identify reliably.

Is MRI really more sensitive than CT in the positive identification of ischaemic stroke?

Studies comparing the sensitivities of CT and MRI would seem to demonstrate that MRI is consistently more sensitive in the positive identification of ischaemic stroke. This is probably the case, but inadequacies in the methodology of the studies make it unsafe to draw very robust conclusions. Sample sizes were small, which make any statistical conclusions drawn vulnerable to the play of chance (see chapter 7). In fact, only one study tested the differences between CT and MRI statistically (finding no significant difference[67]). Blinding the interpreter of images to clinical history or other imaging is essential for maximum objectivity and the prevention of bias, and only 58% of studies comparing CT and MRI were blinded. Perhaps most importantly in these studies, was the timing of CT and MRI in relation to each other. Only one study (8% of studies) varied the order in which scans were performed, and five studies (42%) consistently scanned patients with MRI later (often days later) than CT. Strokes can take days to evolve; if MRI was always performed after CT, it is very likely that it would demonstrate more lesions. To derive the most accurate measure of sensitivity, scans should at the very least be performed on the same day, and ideally (especially in the

hyperacute and acute stages) the order in which they are performed should be randomised.

Sensitivity of CT and MRI in the CT versus MRI study

In our study, scans were performed on the same day. In view of the length of time from stroke to scanning (median 20 days), randomisation of the order of scanning was of less importance than in hyperacute studies. The patients in this study had mild strokes (median Canadian Neurological Score of 9.5), and many had few residual signs. Therefore there were no objective criteria against which to judge scanning in general. In our study, CT and MRI were of equal efficacy overall in demonstrating acute infarction (about 50% of patients), and agreed with each other in a similar proportion (about 70%).

Conclusion

Compared to the number of scans performed routinely on patients with acute stroke, the number of patients involved in these studies is extremely small. This makes significant results vulnerable to chance, and means that studies with serious flaws in their methodology are given more credence than perhaps they deserve. It also means that, as in the identification of intracerebral haemorrhage, we lack robust data on the relative merits of CT and MRI. This renders decisions on the use (or provision) of neuroimaging vulnerable to whim or anecdotal experience. Accumulating a large enough prospective case series with appropriate blinded interpretation of images may be difficult, but would not be impossible. It is also becoming increasingly important to try, as it will not be possible to gauge the significance of new imaging techniques such as diffusion-weighted imaging if we do not have reliable data on the sensitivity of conventional imaging against which to compare it.

Table 1. Studies of the sensitivity of CT in the positive identification of ischaemic stroke – studies where all patients seen by a neurologist/ stroke physician

Study	Date	N of patients	Patient group	Standard	Timing	Sensitivity
Buell[8]	79	159	Stroke - 3 groups - not PICH	Undefined	Hours – 18 to 4 days (gp1), days-28-65(gp2)	0.95
Soderstrom[15]	81	300	Cerebrovascular disease	Clinical progress	Undefined	0.53
Wall[9]	82	26	Acute stroke - not PICH	Clinical progress/autopsy	Hours – 24 or less	0.81
Sandercock[14]	85	325	Suspected stroke, TIA	Clinical progress	Days – 34% in 7/7, 63% in 21/7	0.53
Brott[10]	89	65	Acute stroke - not PICH	Clinical progress	Hours – 48 or less, then 7-10 days	0.4 (admission) 0.77 (10 days)
Sotaniemi[21]	90	1191	Various neurological diseases	Clinical progress	Days - 4 or less (90% of patients)	0.81
Koudstaal[22]	92	1054	Acute stroke (minor), TIA	Undefined	Undefined	0.49
Lindgren[13]	94	228	Acute stroke	Clinical progress	Days - 2 or less, 3-15 (16 later), then 16-30 days	0.47 (admission) 0.74 (3-15 days)
Firlik[16]	97	20	MCA infarcts	Undefined	Hours - less than 6	0.55
Buttner[17]	97	95	MCA infarcts	Clinical progress	Hours – 6 or less	0.47
Al-Buhairi[11]	98	418	Acute stroke - not PICH	Clinical progress	Unclear (60 patients scanned within 48 hours)	0.63
Wardlaw[12]	98	639	Stroke - within 99 days - not PICH	Clinical progress	Days - 7 or less (part of total)	0.60 (day 1) 0.63 (day 7)
Lev[18]	99	30	MCA infarcts	Clinical progress	Hours - 6 or less and control	0.57
Scott[19]	99	39	Acute stroke - thrombolysis recipients	Follow-up scan	Hours - 3 or less	0.64
Barber[20]	2000	117	Acute stroke - thrombolysis recipients - anterior circulation	Clinical progress	Hours - 3 or less and follow-up scan	0.75

Table 2. Studies of the sensitivity of CT in the positive identification of ischaemic stroke – studies where patient groups were not seen by a stroke physician or descriptive only

Study	Date	N of patients	Patient group	Images read blinded?	Study design	Standard	Timing	Sensitivity	Seen by stroke physician
New[69]	74	42	Various neurological diseases	No	Retrospective	Undefined	Undefined	?	No
Jacobs[71]	76	79	Various neurological diseases	No	Unclear	Autopsy	Undefined	?	No
Toghi[72]	81	87	Cerebrovascular disease	Yes**	Unclear	Autopsy	Days - 110 or less	?	No
Sipponen[73]	84	11	Stroke - not PICH	No	Retrospective	Undefined	Days - 1 to 3 months	?	No
Panzer[74]	85	269	Acute stroke	No	Retrospective	None stated	Unclear ('majority scanned within 24 hrs' in RGH)	?	No
Wang[75]	88	530	Suspected stroke - CT scans	No	Retrospective	None stated	Undefined	0.77 (infarcts only)	No
Horowitz[76]	91	50	Acute stroke - not PICH	No	Prospective	Undefined	Hours - 5 or less, then 5-7 days	0.56 initially, 0.74 on follow-up	No
Bendszus[77]	97	45	MCA infarcts	Yes**	Retrospective	Follow-up CT	Hours – 5 or less	0.61 (without DDA) 0.96 with DDA	No
McAlister[68]	97	177	Acute stroke	No	Retrospective	Clinical progress	Hours – within 24 (107), greater than 24 (70)	0.23 (early), 0.58 (delayed scanning)	No
Johansson[78]	84	181	Acute stroke - negative CT	No	Retrospective	Clinical progress	Days - greater than 3	?	Yes
Kinkel[79]	76	111	Cerebrovascular disease	No	Retrospective	Clinical progress	Undefined	?	Yes

Study	Date	N of patients	Patient group	Images read blinded?	Study design	Standard	Timing	Sensitivity	Seen by stroke physician
Inoue[80]	80	30	Acute stroke - positive ischaemic finding on CT	No	Prospective	Undefined	Days - 5 or less	?	Yes
Moulin[81]	96	100	MCA infarcts	Yes**	Retrospective	Clinical progress	Days - 10 or less	?	Yes
Toni[82]	2000	514	Lacunar infarcts	No	Retrospective	Follow-up scan (CT) at 1 week	Hours - less than 6	?	Yes
Toni[83]	95	517	Acute stroke (but investigating sensitivity for lacunar diagnosis)	No	Retrospective	Clinical progress	Days - less than 15	?	Yes

** to clinical history

Table 3. Range of sensitivities of CT in the positive identification of ischaemic stroke; studies grouped according to timing of scanning from onset of stroke symptoms

Timing of scanning	Range of sensitivity of CT	Study reference
Less than 6 hours	0.47 – 0.8	16-20;23
Less than 2 days	0.4 – 0.81	9;10;12;13
Less than 7 days	0.63 – 0.95	8;12;21
Greater than 7 days	0.74 – 0.77	10;13
Undefined	0.49 – 0.63	11;15;22

Table 4. Inter-observer reliability of CT scan interpretation – kappa values

Study	Date	N of patients	Type of CT scan (timing)	Number of observers (type)	Lesion on CT to identify	Images read blinded?	Results
Schneider[26]	91	74	Lacunar syndromes (unspecifed time)	10 (varying in expertise)	Lacunar infarcts, leukoariosis, cerebral atrophy	Yes**	k=0.64 (decreased density), k=0.45 (lacunar infarcts)
Wardlaw[27]	94	119	Patients with acute stroke symptoms (2 hours to 3 months)	8 (2 experts and 6 trainees)	Infarct site, swelling, haemorrhagic transformation	Yes†	k=0.78 (all scans), k=0.87 (medium/large), k=0.59 (small), k=0.8 (swelling), k=0.3 (haemorrhagic transformation)
von Kummer[28]	96	45	CTs with MCA infarct signs and normals (within 6 hours of stroke)	6 neuroradiologists	HMCAS, swelling, parenchymal hypodensity	Yes†	k=0.62/0.57 (HMCAS L/R). k=0.59/0.56 (swelling), k=0.58/0.55 (parenchymal hypodensity)
von Kummer[4]	97	603	CTs of patients randomised in ECASS (within 6 hours)	3 neuroradiologists	Whether recent ischaemia; amount of parenchymal hypoattenuation	Yes**	k=0.34 (recent ischaemia), k=0.36 (amount of swelling)
Gerard[29]	98	33	MAST-E scans (within 6 hours)	3 neurologists	Early infarct signs, intracranial haematoma, haemorrhagic transformation	Yes**	k=1.0 (haematoma), k=1.0 (HTI), k=0.43 (early infarct signs)
Marks[30]	99	50	CTs from patients randomised in ATLANTIS (thrombolysis), (within 6 hours)	3 neuroradiologists	Parenchymal hypodensity, HMCAS	Yes†	k=0.65, 0.44, 0.50 for each pair of observers (hypodensity), k=0.33, 0.2, 0.63 (HMCAS)
Grotta[31]	99	70	CTs from NINDS thrombolysis trial, (within 3 hours)	16 (Emergency physicians, neurologists, radiologists)	Early infarct signs	Yes*	k=0.3 (parenchymal hypodensity), k=0.2 (hypodensity > 33%), k=0.33 (any early sign)

*blind to other imaging, **blind to clinical history, †blind to both

Table 5. Inter-observer reliability of CT scan interpretation – percentage accuracy/ proportion in agreement

Study	Date	N of patients	Type of CT scan	Number of observers (type)	Lesion on CT to identify	Images read blinded?	Results
Roszler[32]	91	289	Emergency room CT	Undefined	Any pathological lesion	No	98% accuracy in interpretation
Alfaro[33]	95	555	Emergency room CT	Undefined (emergency physicians versus radiologists)	Any pathological lesion	No	88.6% accuracy in interpretation
Pullicino[34]	96	20	Infarcts on CT	4 (2 neurologists and 2 neuroradiologists)	Infarct size	No	Intraclass correlation coefficient values used. Overall=0.98
Von Kummer[23]	96	44	Cerebral hemisphere stroke	One	Parenchymal low density and/or focal brain swelling	Yes†	82% sensitivity (36/44) for ischaemia
Schriger[35]	98	15	Selection of old and new infarcts, calcification, haemorrhage, and normal	38 Emergency physicians, 29 neurologists, 36 general radiologists	Infarction (acute of old), haemorrhage, calcification	No	Overall accuracy in interpretation: EPs=67%, neurol=83%, radiol=83%
Kalafut[36]	2000	25	Normals, acute and old infarcts	3 neuroradiologists	Amount of parenchymal hypoattenuation	No	Interpretation of >1/3 MCA territory: 64%; agreement between all 3 moderate

†to clinical history other than 'stroke', and other imaging

Table 6. Studies of the sensitivity of MRI alone in the positive identification of ischaemic stroke, sensitivities available

Study	Date	N of patients	Patient group	Purpose of study	Seen by stroke physician?	Images read blinded?	Sensitivity
Fazekas[41]	96	62	TIA	Clinicotopography	Yes	No	0.31 (acute infarcts)
Cosnard[40]	98	41	Cerebral infarcts	Technical, sensitivity (FLAIR compared with MRA)	Yes	No	0.78
Egelhof[39]	98	34	Ischaemic cerebral infarcts	Clinicotopography (serial scans), sensitivity	Yes	No	0.88 (T2 on first scan)
Razumovsky[38]	99	30	Acute stroke - possible	Sensitivity (with TCD, MRA)	Yes	Yes**	0.73

**blind to clinical history

Table 7. Studies of the sensitivity of MRI alone in the positive identification of ischaemic stroke, sensitivities not available

Study	Date	N of patients	Patient group	Purpose	Seen by stroke physician?	Images read blinded?
Bryan[50]	83	9	Stroke	Technical (exploratory)	Yes	No
Virapongse[51]	86	20	Subacute and chronic stroke	Technical (contrast)	No	No
Kinkel[42]	86	350	Stroke, TIA	Clinicotopography	Yes	No
Byrne[43]	89	76	Brainstem lesions	Clinicotopography	Yes	No
Crain[52]	91	80	Acute stroke	Technical (contrast)	Yes	No
Yuh[44]	91	39	Acute ischaemic stroke	Clinicotopography	Yes	No
Sato[53]	91	8		Technical (contrast)	No	No
Alberts[55]	92	7	Stroke & negative scan	Negative MRI-clinical stroke	Yes	No
Shimosegawa[45]	92	16	Stroke - embolic cerebral infarction	Clinicotopography	Yes	No
Yin[46]	94	81	Infratentorial stroke	Clinicotopography	Yes	No
Kim[47]	94	33	Lateral medullary stroke	Clinicotopography	Yes	No
Brant-Zawadzki[54]	96	50	CVA	Technical (FLAIR)	No	Yes**
Mantyla[48]	99	395	Stroke - WMHI	MR characteristics	Yes	No
Mantyla[49]	99	395	Old stroke	MR characteristics	Yes	Yes

**blind to clinical history

Table 8. Studies of the sensitivity of CT and MRI combined in the positive identification of ischaemic stroke

Study	Date	N of patients	Study type	Images read blinded?	Patient group	Timing	Results
Salgado[56]	86	60	prospective	Yes**	TIA, lacunar or non-lacunar infarct	Days - median 12 (CT) 16 (MRI)	i)CT 4/19 MR 13/19 ii)CT 18/29 MR 21/29 iii) CT 7/12 MR 10/12
Awad[57]	86	22	prospective	Yes**	TIA	Weeks - less than 4 from onset. Scans performed on same or consecutive days	Clinically relevant lesions: MR only 3/22, CT better 2/22
Simmons[62]	86	14	retrospective	No	Cerebellar infarction on MRI	Days - within 14 in 12/14	CT findings on 6/14 (versus 14/14 on MR)
Kertesz[64]	87	175	prospective	Yes*	Acute stroke	Days and weeks - 5 groups see paper. I gp CT/MR within 72 hrs	week 1: MR 71/87, CT 44/87
Rothrock[58]	87	31	prospective	No	Lacunar stroke (acute, subacute, chronic)	Days to 2 years:14 had scans same day	i) MR 11/12, CT 2/12 iii)MR 8/13, CT 4/13
Hommel[59]	88	6	retrospective	No	Lateral medullary infarction	?	CT 2/6 versus MR 5/6
Miyashita[59]	88	9	retrospective	No	Lacunar stroke, multiple infarcts	Days - 7 to 28	Enhanced MR 8/9, CT 4/9
Arboix[61]	90	60	prospective	No	Lacunar infarcts	Hours – 72 to 3 weeks (order unspecified)	MR 78%, CT 30% positive
Bryan[65]	91	31	prospective	Yes**	Acute stroke (clinically definite)	Hours - less than 24 (CT average 4 hrs earlier)	Observer 1: MR 24/31, CT 15/31. Observer 2: MR 27/31, CT 21/31
Arias[66]	92	70	prospective	No	Acute stroke	Days - CT at presentation then MR within 1 week	MR normal in 1/52, CT normal in 25/52

Study	Date	N of patients	Study type	Images read blinded?	Patient group	Timing	Results
Mohr[67]	95	80	prospective	Yes**	Acute stroke	Hours - 68 less than 4, 12 less than 24 (CT first 35, MR first 45)	MR 31/61, CT 26/31 positive (not significant)
Stapf[60]	2000	54	prospective	Yes**	Lacunar stroke	Days - CT less than 2, MR 3-5 days after onset	MR 51/54, CT 27/54

*blind to other imaging, **blind to clinical history

Table 9. Studies of the sensitivity of CT and MRI combined in the positive identification of ischaemic stroke. Patient groups not seen by a stroke physician/neurologist descriptive only

Study	Date	N of patients	Study type	Images read blinded?	Patient group	Timing	Results
Sipponen[84]	83	7	prospective	No	Acute stroke	Days - 4<one, others 7 & 14	Descriptive
Smith[85]	85	55	retrospective	No	Various neurological conditions	Undefined	168 lesions vs 86 MR CT respect, 55 pats
Steinbrich[86]	86	55	undefined	No	Acute stroke	Undefined	'MR demonstrated 11% more infarcts'
Kinkel[42]	86	350	retrospective	No	Cerebrovascular disease	Undefined	Descriptive
Biller[87]	86	10	retrospective	No	Pontine infarction	Hours-CT within few hours of hospitalisation, MR unclear	CT 1/10; MR 9/10
Cirillo[88]	88	192	retrospective	No	Various neurological conditions	Undefined	MR identified 23 infarcts not seen on CT
Brown[89]	88	21	prospective and retrospective	No	'Lacunar TIAs or strokes of varying chronicity'	Days - 'acute' < 3/7, subacute < 30/7, chronic >3/12	TIAs: MR 24/25, CT 10/25, recent: MR 13/13, CT 0/12
Imakita[90]	88	35	prospective	No	Confirmed or suspected cerebral infarction	Hours - 4 to 27 months	MR enhancement was 'more obvious, more extensive'
Hommel[91]	90	100	prospective	No	Lacunar stroke	Days - CT within 4, MR on average 18 days after stroke	MR showed compatible lesions in 89%
Shuaib[92]	92	116	retrospective	No	Acute stroke	Days - both done within 10	MR changed management in 18.9%
Krivoshapkin[93]	92	16	pro	No	Patients with EC-IC bypass	Undefined	Descriptive
Boyko[94]	92	12	retrospective	No	Hyperintensities on T1	Undefined	Descriptive

Study	Date	N of patients	Study type	Images read blinded?	Patient group	Timing	Results
Fiorelli[95]	93	2	prospective	No	Acute stroke	Hours - <4, scans within hour of each other	Descriptive
Maeda[96]	99	1	Case report	No	Acute right hemiparesis	Hours – less than 3	Lesion seen on both

Table 10. Sensitivity of CT and MRI in the positive identification of ischaemia in unselected strokes

Study	Proportion of images demonstrating clinically compatible lesion (%)	
	CT	MRI
Kersetz[64]	51	82
Bryan[65]:		
Observer 1	48	77
Observer 2	68	87
Arias[66]	52	98
Mohr[67]	43	51

Table 11. Sensitivity of CT and MRI in the positive identification of ischaemic lacunar stroke

Study	Proportion of images demonstrating clinically compatible lesion (%)	
	CT	MRI
Rothrock[58]	17	92
Miyashita[59]	44	89
Arboix[61]	30	78
Stapf[60]	50	94

Table 12. CT versus MRI study. CT showed recent infarct, corresponding MRI findings

Scan findings	Number of findings on MRI (%)
Recent infarct	86 (72.2)
Recent infarct & haemorrhagic transformation	10 (8.4)
Recent haemorrhage	5 (4.2)
Old lesion probable infarct	2 (1.7)
Old lesion probable haemorrhage	2 (1.7)
Multiple periventricular lucencies and/or cortical atrophy	10 (8.4)
Tumour	0 (0)
No abnormality	4 (3.4)
Total	119

Table13. CT versus MRI study. MRI showed recent infarct, corresponding CT findings.

Scan findings	Number of findings on CT (%)
Recent infarct	86 (70.5)
Recent infarct & haemorrhagic transformation	0 (0)
Recent haemorrhage	0 (0)
Old lesion probable infarct	8 (6.6)
Old lesion probable haemorrhage	0 (0)
Multiple periventricular lucencies and/or cortical atrophy	15 (12.3)
Tumour	1 (0.8)
No abnormality	12 (9.8)
Total	122

1. Wardlaw, J. M., Yamaguchi, T., and del Zoppo, G. J. Thrombolytic therapy versus control in acute ischaemic stroke (Cochrane Review). The Cochrane Library (3). 1998. Oxford, Update software.

2. Tilley BC, Lyden PD, Brott TG, Lu M, Levine SR, Welch KM. Total quality improvement method for reduction of delays between emergency department admission and treatment of acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Archives of Neurology 1997;54:1466-74.

3. Chiu D, Krieger D, Villar-Cordova C, Kasner SE, Morgenstern LB, Bratina et al. Intravenous tissue plasminogen activator for acute ischemic stroke: feasibility, safety, and efficacy in the first year of clinical practice. Stroke 1998;29:18-22.

4. von Kummer R, Allen KL, Holle R, Bozzao L, Bastianello S, Manelfe C et al. Acute stroke: usefulness of early CT findings before thrombolytic therapy [see comments]. Radiology 1997;205:327-33.

5. Krieger D, Demchuk AM, Kasner SE, Jauss M, Hantson L. Early clinical and radiological predictors of fatal brain swelling in ischaemic stroke. Stroke 1999;30:287-92.

6. Grond M, von Kummer R, Sobesky J, Schmulling S, Rudolf J, Terstegge K et al. Early Xray hypoattenuation of brain parenchyma indicates extended critical hypoperfusion in acute stroke. Stroke 2000;31:133-9.

7. Russell EJ. Diagnosis of hyperacute ischemic infarct with CT: key to improved clinical outcome after intravenous thrombolysis? [editorial; comment]. Radiology 1997;205:315-8.

8. Buell U, Kazner E, Rath M, Steinhoff H, Kleinhans E, Lanksch W. Sensitivity of computed tomography and serial scintigraphy in cerebrovascular disease. Radiology 1979;131:393-8.

9. Wall SD, Brant-Zawadzki M, Jeffrey RB, Barnes B. High frequency CT findings within 24 hours after cerebral infarction. AJR 1982;138:307-11.

10. Brott T, Marler JR, Olinger CP, Adams HP, Tomsick T. Measurements of acute cerebral infarction: lesion size by computed tomography. Stroke 1989;20:871-5.

11. Al-Buhari AR, phillips SJ, Llwellyn G, Jan MSJ. Prediction of infarct topography using the Oxfordshire Community Stroke Project classification of stroke subtypes. J Stroke Cerebrovasc Dis 1998;7:339-43.

12. Wardlaw JM, Lewis SC, Dennis MS, Counsell C, McDowall M. Is visible infarction on computed tomography associated with an adverse prognosis in acute ischemic stroke? Stroke 1998;29:1315-9.

13. Lindgren A, Norrving B, Rudling O, Johansson BB. Comparison of clinical and neuroradiological findings in first-ever stroke. A population-based study. Stroke 1994;25:1371-7.

14. Sandercock P, Molyneux A, Warlow C. Value of computed tomography in patients with stroke: Oxfordshire Community Stroke Project. Br.Med.J (Clin.Res.Ed) 1985;290:193-7.

15. Soderstrom CE, Ericson K, Mettinger KL, Olivecrona H. Computed tomography and CSF spectrophotometry. Diagnosis and prognosis in 300 patients with cerebrovascular disease. Scandinavian Journal of Rehabilitation Medicine 1981;13:65-71.

16. Firlik AD, Kaufmann AM, Wechsler LR, Firlik KS, Fukui MB, Yonas H. Quantitative cerebral blood flow determinations in acute ischemic stroke. Relationship to computed tomography and angiography. Stroke 1997;28:2208-13.

17. Buttner T, Uffmann M, Gunes N, Koster O. Early CCT signs of supratentorial brain infarction: clinico- radiological correlations. Acta Neurol Scand 1997;96:317-23.

18. Lev MH, Farkas J, Gemmete JJ, Hossain ST, Hunter GJ, Koroshetz WJ et al. Acute stroke: improved nonenhanced CT detection--benefits of soft-copy interpretation by using variable window width and center level settings. Radiology 1999;213:150-5.

19. Scott JN, Buchan AM, Sevick RJ. Correlation of neurological dysfunction with CT findings in early acute stroke. Can J Neurol Sci 1999;26:182-9.

20. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet 2000;355:1670-4.

21. Sotaniemi KA, Phytinen J, Myllyla VV. Correlation of clinical and computed tomographic findings in stroke patients. Stroke 1990;21:1562-6.

22. Koudstaal PJ, van Gijn J, Frenken CW, Hijdra A, Lodder J, Vermeulen M et al. TIA, RIND, minor stroke: a continuum, or different subgroups? Dutch TIA Study Group. J.Neurol.Neurosurg.Psychiatry 1992;55:95-7.

23. von Kummer R, Nolte PN, Schnittger H, Thron A, Ringelstein EB. Detectability of cerebral hemisphere ischaemic infarcts by CT within 6 h of stroke. Neuroradiology 1996;38:31-3.

24. Warlow CP, Dennis MS, van Gijn J, Hankey GJ, Sandercock PAG, Bamford JM et al. What pathological type of stroke is it? Stroke: a practical guide to management, pp 151-222. Oxford: Blackwell Scientific Ltd, 2001.

25. Brennan P,.Silman A. Statistical methods for assessing observer variability in clinical measures. BMJ 1992;304:1491-4.

26. Schneider R, Kluge R, Willmes K. Interrater agreement for CT scans of patients with lacunar infarcts and leuko-araiosis. Acta Neurol Scand 1991;84:527-30.

27. Wardlaw J,.Sellar R. A simple practical classification of cerebral infarcts on CT and its interobserver reliability. Am J Neuroradiol 1994;15:1933-9.

28. von Kummer R, Holle R, Gizyska U, Hofmann E, Jansen O, Petersen D et al. Interobserver agreement in assessing early CT signs of middle cerebral artery infarction. Ajnr: American Journal of Neuroradiology 1996;17:1743-8.

29. Besson G, Moulin T, Chavot D, Tatu L, Garnier P, Crepin-Leblond T. Intra-observer concordance of the neuroradiologic reviewing committee in CT scan reviewing in MAST-E. Acta Neurol Scand 1998;98:292-3.

30. Marks MP, Holmgren EB, Fox AJ, Patel S, von Kummer R, Froehlich J. Evaluation of early computed tomographic findings in acute ischemic stroke. Stroke 1999;30:389-92.

31. Grotta JC, Chui D, Lu M, Patel S, Levine SR. Agreement and variability in the interpretation of early CT changes in stroke patients qualifying for intravenous rTPA therapy. Stroke 1999;30:1528-33.

32. Roszler MH, McCarroll KA, Rashid T, Donovan KR, Kling GA. Resident interpretation of emergency computed tomographic scans. Investigative Radiology 1991;26:374-6.

33. Alfaro D, Levitt MA, English DK, Williams V, Eisenberg R. Accuracy of interpretation of cranial computed tomography scans in an emergency medicine residency program. Annals of Emergency Medicine 1995;25:169-74.

34. Pullicino P, Snyder W, Munschauer F, Pordell R, Greiner F. Interrater agreement of computed tomography infarct measurement. Journal of Neuroimaging 1996;6:16-9.

35. Schriger DL, Kalafut M, Starkman S, Krueger M, Saver JL. Cranial computed tomography interpretation in acute stroke: physician accuracy in determining eligibility for thrombolytic therapy. JAMA 1998;279:1293-7.

36. Kalafut MA, Schriger DL, Saver JL, Starkman S. Detection of early CT signs of >1/3 middle cerebral artery infarctions : interrater reliability and sensitivity of CT interpretation by physicians involved in acute stroke care. Stroke 2000;31:1667-71.

37. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA 1995;274:1017-25.

38. Razumovsky AY, Gillard JH, Bryan RN, Hanley DF, Oppenheimer SM. TCD, MRA and MRI in acute cerebral ischemia. Acta Neurol Scand 1999;99:65-76.

39. Egelhof T, Essig M, von Kummer R, Dorfler A, Winter R, Sartor K. Acute ischemic cerebral infarct: prospective serial observations by magnetic resonance imaging. Rofo 1998;Fortschritte auf dem Gebiete der Rontgenstrahlen und der Neuen Bildgebenden Verfahren. 168:222-7.

40. Cosnard G, Duprez T, Grandin C, Smith AM, Munier T, Peeters A. Fast FLAIR sequence for detecting major vascular abnormalities during the hyperacute phase of stroke: a comparison with MR angiography. Neuroradiology 1999;41:342-6.

41. Fazekas F, Fazekas G, Schmidt R, Kapeller P, Offenbacher H. Magnetic resonance imaging correlates of transient cerebral ischemic attacks. Stroke 1996;27:607-11.

42. Kinkel PR, Kinkel WR, Jacobs L. Nuclear magnetic resonance imaging in patients with stroke. Seminars in Neurology 1986;6:43-52.

43. Byrne JV, Kendall BE, Kingsley DPE, Moseley IF. Lesions of the brain stem: Assessment by magnetic resonance imaging. Neuroradiology 1989;31:129-33.

44. Yuh WTC, Crain MR, Loes DJ, Greene GM, Ryals TJ, Sato Y. MR imaging of cerebral ischaemia: findings in the first 24 hours. Am J Neuroradiol 1991;12:621-9.

45. Shimosegawa E, Inugami A, Okudera T, Hatazawa J, Ogawa T, Fujita H et al. Embolic cerebral infarction: MR findings in the first 3 hours after onset. AJR 1993;American Journal of Roentgenology. 160:1077-82.

46. Yin W-M, Nagata K, Satoh Y, Yokoyama E, Watahiki Y, Yuya H et al. Infratentorial infarction: Correlation of MR findings with neurological and angiographical features. Neurological Research 1994;16:154-8.

47. Kim JS, Lee JH, Suh DC, Lee MC. Spectrum of lateral medullary syndrome: Correlation between clinical findings and magnetic resonance imaging in 33 subjects. Stroke 1994;25:1405-10.

48. Mantyla R, Aronen HJ, Salonen O, Korpelainen M, Peltonen T, Standertskjold-Nordenstam C. The prevalence and distribution of white-matter changes on different MRI pulse sequences in a post-stroke cohort. Neuroradiology 1999;41:657-65.

49. Mantyla R, Aronen HJ, Salonen O, Pohjasvaara T, Korpelain M, Peltonen T. Magnetic resonance imaging white matter hyperintensities and mechanism of ischemic stroke. Stroke 1999; 30:2053-8.

50. Bryan RN, Willcott MR, Schneiders NJ. Nuclear magnetic resonance evaluation of stroke. A preliminary report. Radiology 1983;149:189-92.

51. Virapongse C, Mancuso A, Quisling R. Human brain infarcts: Gd-DTPA-enhanced MR imaging. Radiology 1986;161:785-94.

52. Crain MR, Yuh WTC, Greene GM, Loes DJ, Ryals TJ, Sato Y. cerebral ischaemia: evaluation with contrast-enhanced MR imaging. Am J Neuroradiol 1991;12:631-9.

53. Sato A, Takahashi S, Soma Y, Ishii K, Kikuchi Y, Watanabe T et al. Cerebral infarction: early detection by means of contrast-enhanced cerebral arteries at MR imaging. Radiology 1991;178:433-9.

54. Brant-Zawadzki M, Atkinson DJ, Detrick M, Bradley WG, Scidmore G. fluid-attenuated inversion recovery (FLAIR) for assessment of cerebral infarction. Initial cllinical experience in 50 patients. Stroke 1996;27:1187-91.

55. Alberts MJ, Faulstich ME, Gray L. Stroke with negative brain magnetic resonance imaging. Stroke 1992;23:663-7.

56. Salgado ED, Weinstein M, Furlan AJ, Modic MT, Beck GJ, Estes M et al. Proton magnetic resonance imaging in ischemic cerebrovascular disease. Ann.Neurol. 1986;20:502-7.

57. Awad I, Modic M, Little JR, Furlan AJ, Weinstein M. Focal parenchymal lesions in transient ischemic attacks: correlation of computed tomography and magnetic resonance imaging. Stroke 1986;17:399-403.

58. Rothrock JF, Lyden PD, Hesselink JR, Brown JJ, Healy ME. Brain magnetic resonance imaging in the evaluation of lacunar stroke. Stroke 1987;18:781-6.

59. Miyashita K, Naritomi H, Sawada T, Nakamura M, Kuriyama Y, Ogawa M. Identification of recent lacunar lesions in cases of multiple small infarctions by magnetic resonance imaging. Stroke 1988;19:834-9.

60. Stapf C, Hofmeister C, Hartmann A, Marx P, Mast H. Predictive value of clinical lacunar syndromes for lacunar infarcts on magnetic resonance brain imaging. Acta Neurol Scand 2000;101:13-8.

61. Arboix A, Marti-Vilalta JL, Pujol J, Sanz M. Lacunar cerebral infarct and nuclear magnetic resonance. A review of sixty cases. Eur.Neurol. 1990;30:47-51.

62. Simmons Z, Biller J, Adams HP, Jr., Dunn V, Jacoby CG. Cerebellar infarction: comparison of computed tomography and magnetic resonance imaging. Ann Neurol 1986;19:291-3.

63. Hommel M, Pollak P, Gaio JM, Besson G, Borgel F, Le Bas JF et al. Magnetic resonance imaging in lateral medullary infarction. Revue Neurologique 1988; 144:272-8.

64. Kertesz A, Black SE, Nicholson L, Carr T. The sensitivity and specificity of MRI in stroke. Neurology 1987;37:1580-5.

65. Bryan RN, Levy LM, Whitlow WD, Killian JM, Preziosi TJ, Rosario JA. Diagnosis of acute cerebral infarction: comparison of CT and MR imaging. Ajnr: American Journal of Neuroradiology 1991;12:611-20.

66. Arias M, Requena I, Pereiro I, Amigo ME, Ventura M, Quintans L et al. CT vs MRI in the diagnosis of acute stroke. Archivos de Neurobiologia 1992;55:50-6.

67. Mohr JP, Biller J, Hilal SK, Yuh WTC, Tatemichi TK, Hedges S. Magnetic resonance versus computed tomographic imaging in acute stroke. Stroke 1995;26:807-12.

68. McAlister FA, Fisher BW, Houston SC. The timing of computed tomography in acute stroke: a practice audit. Canadian Association of Radiologists Journal 1997;48:123-9.

69. New PJF, Scott WR, Schnur JA, Davis KR, Taveras JM. Computerized axial tomography with the EMI scanner. Radiology 1974;110:109-23.

70. Paxton R,.Ambrose J. EMI scanner: brief review of first 650 patients. Br.J.Radiol. 1974;47:530-65.

71. Jacobs L, Kinkel WR, Heffner RR, Jr. Autopsy correlations of computerized tomography: experience with 6,000 CT scans. Neurology 1976;26:1111-8.

72. Toghi H, Mochizuki H, Yamanouchi H, Iio M, Yamada H, Chiba K et al. A comparison between the computed tomogram and the neuropathological findings in cerebrovascular disease. J Neurol 1981;224:211-20.

73. Sipponen JT. Visualization of brain infarction with nuclear magnetic resonance imaging. Neuroradiology 1984;26:387-91.

74. Panzer RJ, Feibel JH, Barker WH, Griner PF. Predicting the likelihood of hemorrhage in patients with stroke. Arch.Intern.Med. 1985;145:1800-3.

75. Wang AM, Lin JC, Rumbaugh CL. What is expected of CT in the evaluation of stroke? Neuroradiology 1988;30:54-8.

76. Horowitz SH, Zito JL, Donnarumma R, Patel M. Computed tomographic-angiographic findings within the first five hours of cerebral infarction. Stroke 1991;22:1245-53.

77. Bendszus M, Urbach H, Meyer B, Schultheiss R, Solymosi L. Improved CT diagnosis of acute middle cerebral artery territory infarcts with density-difference analysis. Neuroradiology 1997;39:127-31.

78. Johansson T. Cerebral infarctions with negative CT scans. Eur.Neurol. 1984;23:124-31.

79. Kinkel WR,.Jacobs L. Computerized axial transverse tomography in cerebrovascular disease. Neurology 1976;26:924-30.

80. Inoue Y, Takemoto K, Miyamoto T, Yoshikawa N, Taniguchi S, Saiwai S. Sequential computed tomography scans in acute cerebral infarction. Radiology 1980;135:655-62.

81. Moulin T, Cattin F, Crepin-Leblond T, Tatu L, Chavot D, Piotin M et al. Early CT signs in acute middle cerebral artery infarction: predictive value for subsequent infarct locations and outcome. Neurology 1996;47:366-75.

82. Toni D, Iweins F, von Kummer R, Busse O, Bogousslavsky J, Falcou A et al. Identification of lacunar infarcts before thrombolysis in the ECASS I study. Neurology 2000;54:684-8.

83. Toni D, Fiorelli M, De Michele M, Bastianello S, Sacchetti ML, Montinaro et al. Clinical and prognostic correlates of stroke subtype misdiagnosis within 12 hours from onset. Stroke 1995;26:1837-40.

84. Sipponen JT, Kaste M, Ketonen L, Sepponen RE, Katevuo K, Sivula A. Serial nuclear magnetic resonance (NMR) imaging in patients with cerebral infarction. J Comput Assist Tomography 1983;7:585-9.

85. Smith AS, Weinstein MA, Modic MT. Magnetic resonance with marked T2-weighted images: improved demonstration of brain lesions, tumor, and edema. AJR 1985;145:949-55.

86. Steinbrich W, Friedmann G, Pawlik G, Bocher-Schwarz HG, Heiss WD. MR of ischemic brain diseases. A comparison with CT, PET (18-fluorodeoxyglucose) and angiographic results. Rofo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin 1986; 145:173-81.

87. Biller J, Adams HP, Dunn V, Simmons Z, Jacoby CG. Dichotomy between clinical findings and MR abnormalities in pontine infarction. J Comput Assist Tomography 1986;10:379-85.

88. Cirillo S, Simonetti L, La Tessa G, Elefante R, Smaltino F. MR imaging and CT: Comparative adequacy in neuroradiology. Radiologia Medica 1988;76:(pp 390-8).

89. Brown JJ, Hesselink JR, Rothrock JF. MR and CT of lacunar infarcts. AJR 1988;American Journal of:367-72.

90. Imakita S, Nishimura T, Yamada N, Naito H, Takamiya M, Yamada Y et al. Magnetic resonance imaging of cerebral infarction: time course of Gd-DTPA enhancement and CT comparison. Neuroradiology 1988;30:372-8.

91. Hommel M, Besson G, Le Bas JF, Gaio JM, Pollak P, Borgel F et al. Prospective study of lacunar infarction using magnetic resonance imaging. Stroke 1990;21:546-54.

92. Shuaib A, Lee D, Pelz D, Fox A, Hachinski VC. The impact of magnetic resonance imaging on the management of acute ischemic stroke. Neurology 1992;42:816-8.

93. Krivoshapkin AL, Jacobson MG, Rabinovich SS. Correlation of MRI and CT data with outcome of cerebral revascularization after stroke. Neurological Research 1992;14:211-3.

94. Boyko OB, Burger PC, Shelburne JD, Ingram P. Non-heme mechanisms for T1 shortening: Pathologic, CT, and MR elucidation. Am J Neuroradiol 1992;13:1439-45.

95. Fiorelli M, Sacchetti ML, Toni D, Argentino C, Gori C, Di Biasi C et al. Feasibility and usefulness of conventional spin-echo MR imaging in hyperacute ischemic stroke: A comparison with CT scan. Circulation et Metabolisme du Cerveau 1993;10:5-10.

96. Maeda M, Abe H, Yamada H, Ishii Y. Hyperacute infarction: A comparison of CT and MRI, including diffusion-weighted imaging. Neuroradiology 1999;41:175-8.

7 The Sensitivity Of Diffusion-Weighted Imaging And Perfusion Imaging In The Identification Of Ischaemic Stroke.

7.1 Introduction

Why do we need better imaging techniques in stroke care?

When thrombolysis began to be used in stroke, it was hoped that by reopening acutely occluded arteries, thrombolytic agents would produce a clinical improvement that was so obvious that the clinician at the bedside would see it. Although this can happen, in the majority of patients the immediate effects are not that obvious[1]. Also, as more patients are seen in the hyperacute phase, spontaneous early improvements are more often seen. To gauge whether any potential new treatment is effective, we currently rely on patient clinical outcome measures like death or functional outcome. These are obviously the most relevant factor to patients, carers and care-providers, but clinical outcome may require large numbers of patients i.e. it may not be sensitive enough to demonstrate a potentially encouraging physiological effect of a treatment, which following refinement may prove to be clinically beneficial.

Advanced imaging techniques such as magnetic resonance diffusion-weighted imaging (DWI) and perfusion imaging (PI, which can be performed on both MR and CT scanners) may prove useful in this area of stroke research, as well areas with more direct clinical relevance. Consequently, considerable enthusiasm has been expressed for these techniques[2;3]. The combination of DWI and PI (combined in one appealing imaging sequence on MRI) may provide important detail on the status of the damaged brain.

Principles of diffusion weighted imaging

DWI makes use of the fact that molecules are in a constant state of (Brownian) motion. By applying a series of two sequential gradient pulses to a conventional MRI sequence, molecules moving after the pulse has been applied acquire phase shifts that lead to the failure of such molecules to rephase completely, the molecule of interest for biological scanning purposes generally being water. This effect can be measured, the resulting signal being interpreted on a scan as an area of altered intensity[4]. The amount of signal

remaining after application of the second gradient pulse is related to two factors: the diffusion coefficient of the substance and duration and strength of the magnetic field gradients. This relationship was originally described by two physical chemists, Stejskal and Tanner, as follows:

$$SD \propto e^{-bD}$$

SD = degree of signal drop

D = diffusion coefficient

b = duration and strength of the (encoding) gradient

Effectively, it means that for a given encoding gradient, substances with high diffusion coefficients lose signal more rapidly than those with a low diffusion coefficient. In a region of infarcted tissue, the diffusion of water molecules is restricted and will therefore undergo signal loss more slowly than surrounding normal tissue (resulting in increased signal on imaging).

By obtaining images with gradients of different strengths (multiple b values, two readings giving the necessary accuracy), an apparent diffusion coefficient (ADC) can be calculated, providing a quantitative measurement of water motion independent of magnetic field strength and gradient. Because molecules can theoretically move in any direction, the measurement of ADC is a three-dimensional quantity, known as a tensor (as opposed to a scalar or vector quantity). It is the *apparent* diffusion coefficient that is measured, rather than the true diffusion coefficient because of the uncertainty surrounding the origin of water mobility. The ADC also takes into account the fact that the movement of water molecules in a biological system is not truly random, rather there is constraint along tissue planes, making movement in one direction easier than another ('diffusion anisotropy'). If anisotropy is not taken into account, results can be misleading; for instance, while ADC values (i.e. the average mobility) is similar for water molecules in both grey and white matter, white matter shows a strong directional preponderance. Measuring ADC values in only one plane would therefore lead to misleading values which would depend upon the ease with which water molecules could move in that plane, a factor not recognised in early diffusion studies[5]. This problem is solved by sampling the ADC in at least three different directions. Also, as well as the direction in which water molecules move not being truly random, the degree to which they move is dependent on exogenous factors. One of the most clinically

relevant factors is the level of energy in the system, with molecules moving more at higher temperatures[6].

Principles of Perfusion Imaging

Perfusion imaging can detect hypoperfused regions of brain either by monitoring the transit of a rapidly injected contrast agent[7] or magnetically tagged water molecules in arterial blood[8] through the brain. In regions distal to an arterial occlusion, the arrival of the contrast agent or tagged water molecules may be delayed. The resulting signal-time curve can be converted into a concentration-time curve, from which several functions that describe regional perfusion can be determined.

The need for a systematic review on diffusion and perfusion imaging

The ease with which ischaemia can be identified on DWI compared to CT and conventional MRI can be striking (figure 1). However, as has been discussed, before a new imaging procedure is introduced for use in a general population, it should have been demonstrated that images such as these are reproducible in the general population rather than a highly selected case series.

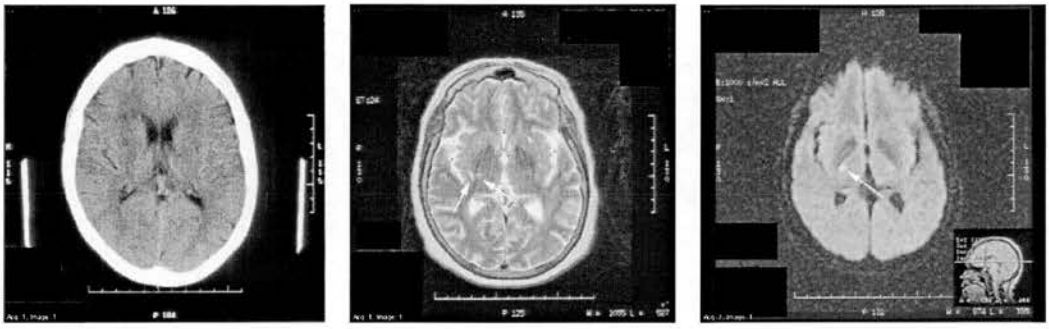


Figure 1. CT (left), conventional MRI (T2-weighted, middle) and DWI (right) scans performed within 24 hours of each other, of a patient with sudden onset left leg weakness and left arm tingling. Note no identifiable area of hypodensity on CT, various areas of increased signal on T2 MR but none distinguishing, and obvious small area of increased signal in the right internal capsule on DWI (arrows).

Not only should DWI and PI produce reliable and accurate results, but they should also be clinically feasible and ideally have a positive therapeutic impact[9]. In recent years, the enthusiasm for DWI and PI has grown with a consequent explosion of publications on these techniques. Are they an improvement on CT or standard MRI techniques in the

investigation of stroke? What information has been obtained so far on patient characterisation that was previously not readily available? Have they had any effect on acute stroke treatment guidance? To find out whether these questions had been addressed, as well as determining the methodological quality of studies published so far, and to identify where more information might be needed, a systematic review of magnetic resonance DWI and PI was performed.

7.2 Methods

Search strategy

An electronic search was performed for all published articles on DWI, PI or a combination of the two, in the English and non-English language literature in Medline and Embase from 31st October 1999 back to the earliest studies available (1990). The Cochrane library extended search strategy for stroke (appendix III) was combined with the search terms: 'diffusion weighted', 'perfusion weighted', 'dynamic susceptibility', 'haemodynamically weighted', expanded to maximise the number of hits. Also, six relevant journals (Stroke, Radiology, American Journal of Neuroradiology, American Journal of Roentgenography, Magnetic Resonance in Medicine, Journal of Magnetic Resonance Imaging) were hand-searched from November 1999 to January 2000, and reference lists were examined from all the identified studies. The inclusion criteria were published studies in which DWI, PI or both in combination had been conducted in humans with stroke. Case reports and studies that had so far only appeared in abstract form were excluded. A further search was performed in April 2001. Although the data from the first search will be the main subject of this chapter, any important findings in later studies will be highlighted.

Data extraction and analysis

Information was extracted on: the sample size of each study; its main purpose, the time window from onset of stroke symptoms to imaging, how the diagnosis of stroke had been made and by whom, the patient inclusion criteria, the DWI or PI scanning method, the image analysis method, whether interpretation of diffusion or perfusion images was blinded to clinical details and the results of other imaging modalities, whether any patients had been imaged but then excluded from further analysis and

why; whether any data on clinical outcome had been collected and at what time after stroke, and the overall conclusion of the study. The extracted information was entered into an Access database and assessed with descriptive statistics.

7.3 Results

7.3.1 Studies of diffusion-weighted imaging alone

Identified studies and general methodological details

Searching captured 50 studies concerned specifically with DWI in humans with ischaemic stroke (2342 patients, median sample size 32). In these studies, although the technical information on the imaging sequences was good, the information on general methodological details (blinding, patient selection and exclusions, and the proportion of uninterpretable scans) was limited, and generally these details were not mentioned. In only 10/50 (20%) were scans interpreted blinded to clinical details or other imaging[10-18;70], and only seven (14%) gave specific details on patient inclusions and exclusions[16;17;19-23]. Only nine studies gave details on the number (and reasons for) inadequate scans that were excluded from further analysis[16;17;19;21;24-28], although it is likely that patients with poor quality scans were excluded from the analysis in other studies. There were no details in any of the studies on patient tolerability of the investigation or evaluation of the risk to the patient. Table 1 lists the fifty studies concerning DWI alone identified, with their primary purpose and main findings. The majority of studies were performed in association with departments with an interest in stroke.

Primary purposes of identified studies

Studies of a technical nature

Seventeen studies (567 patients) investigated DWI techniques or refinements of techniques of image acquisition of processing, methods of calculations of the ADC[14;16;19;24-26;28-38]. No useful comparisons could be made between them as all covered different aspects and mentioned little about the type of patients included.

DWI lesions at differing time points

Six studies (564 patients) studied the visibility of DWI lesions or changes in ADC values over time. In five, the proportions of patients where repeated scanning was completed successfully were limited[39-41] or impossible to determine[15;42]. In these studies, the time over which lesions remained visible on DWI was inferred by using scans of different patients at different time points, rather than repeated imaging of the same patients. In only one study were the majority of patients repeatedly scanned, and it found reduced ADC values for up to 85 days after stroke[21].

DWI lesions, neurological disability and clinical outcome

Two studies (92 patients) investigated the correlation of early DWI (within 24 and 60 hours) with measures of clinical stoke severity at the time of imaging and at a later date (three and 42 weeks)[12;17]. Both studies demonstrated that acute lesion volumes on DWI correlated with both the National Institute of Health Scale (NIHSS) (both acutely and at follow-up) and the modified Rankin Scale (RS) at follow-up. In both studies, images were read blinded to clinical details, and in one also to initial T2-WI.

DWI compared to CT and conventional MRI

Thirteen studies (457 patients) suggested that DWI demonstrated more lesions in the symptomatic anatomical area at an earlier time-point than did conventional imaging. Although one study directly compared CT and DWI (17 patients)[10], the majority of studies compared DWI to conventional MRI[15;18;27;41;43-50]. All indicated that more lesions were visible on DWI than conventional imaging. Timing of scanning varied between studies from: less than six hours[10;15;41;44;46], within 48 hours[45;47], within 4 days[18;43], to 'the time period under investigation (eight hours to 12 days)[27]. Scans were interpreted blinded to clinical details in only two studies[15;18], to other imaging in only one[44], and to both imaging and clinical details in only one[10]. No study randomised the order, or even stated the order in which scans were performed. Sample sizes ranged from 103 to only nine patients. The proportion of patients in which DWI was felt to be superior to conventional MR imaging ranged from five to 71%. In one study, it was impossible to define in how many patients DWI had proven superior[48].

Differentiating new from old lesions on DWI

Eight studies (454 patients) found that in patients with multiple lesions of MRI, it was possible to distinguish new from old lesions with DWI[16;18;27;42;51-54]. Acute lesions appeared hyper-intense, and old lesions hypo-intense. Timing of scanning in these studies ranged from less than seven hours to 11 days. In only two studies were the scans read blinded to clinical details[16;18]. The proportion of patients where DWI was felt to be superior in distinguishing new from old lesions compared with conventional MRI ranged from four to fifteen of 220 patients with multiple lesions, i.e. less than 10% the total number of patients included.

Clinicotopography of DWI lesions

Six studies (261 patients) concentrated on the clinicotopography of a specific stroke subtype such as lacunar stroke[55-58] or transient ischaemic attack[59;60]. The studies concentrating on lacunar symptoms demonstrated that DWI could identify appropriate subcortical areas of ischaemia. One study (62 patients) noted that 16% of patients presenting with lacunar syndrome had multiple lesions identified on DWI[58]. One study concerned with transient ischaemic attacks demonstrated that 48% of patients whose symptoms resolved within 24 hours had relevant lesions on DWI within 24 hours of symptom onset. Patients whose symptoms resolved by 24 hours had smaller and less obvious lesions on DWI than patients whose symptoms had lasted longer[59].

Feasibility of a DWI scanning protocol

Six studies (13%, 518 patients), two of which were retrospective analyses, addressed the feasibility of undertaking an advanced imaging protocol in acutely ill stroke patients and suggested that it was possible[59;61-65]. None of the imaging was read blinded, which is clinically realistic, but data on patient inclusion and exclusions, as well as clinical characteristics was often limited, i.e. information to identify patients who would be poor subjects for DWI, or any problems that were encountered were not given. Two studies (20 patients) demonstrated that it was possible to identify acute haemorrhage, a subset of patients previously thought to present difficulty on DWI[66;67]. However, neither study was blinded to other imaging results.

False negatives and inter-observer reliability of image analysis

One retrospective study (27 patients) raised the important issue of patients with stroke-like deficits and negative DWI imaging[68] and described their case series. They explained that specificity had not been addressed because their entire (and substantial) case series (782 patients) had not been reviewed. One study (19 patients) investigated the inter-observer reliability of DWI in the detection of greater than a third involvement of the middle cerebral artery in ischaemic stroke compared to CT[69]. Lesions were identified correctly in all cases on DWI, compared to between 42 and 63% of those on CT. DWI scans were performed on average 2.6 hours after CT. One study explored the yield of potentially relevant information on DWI, noting clinically significant findings on DWI alone in 48% of patients. In the discussion, they mentioned that 'the active clinical relevance was not addressed'. Of note was the observation that 9/40 (23%) of patients refused follow-up scanning at 30 days[70].

7.3.2 Studies of perfusion imaging alone

Included studies

Fourteen studies concerning MR PI alone were identified (198 patients, median 10), as well as four studies combining MR PI with another advanced imaging modality such as single photon emission computed tomography (SPECT) (38 patients, median 10).

MR PI alone

Of the 14 studies concerning PI alone, one study (15 patients) attempted to evaluate the clinical usefulness of PWI[71]. The other 13 studies (183 patients) were concerned with the technical aspects of demonstrating abnormalities of regional cerebral perfusion[7;8;72-82]. All bar one[81], which attempted to quantify the arterial input function, a constant required for the calculation of absolute blood flow, assessed relative rather than absolute cerebral blood flow. All studies used the gadolinium bolus tracking method of measuring blood transit time. A variety of perfusion abnormalities were demonstrated; one study (11 patients) noted a heterogeneous distribution of rCBF in the expected regions of interest in all examinations[73]; three studies (102 patients) documented hyperperfusion as well as delayed or absent perfusion in the region of interest [7;8;72]; and

one study (11 patients) documented no perfusion deficits in four out of the eleven subjects despite marked clinical signs and repeat MRI within 48 hours confirming infarction[71].

MR PI combined with other imaging modalities

Of the four studies that combined MR PI with another advanced imaging modality, perfusion MRI was correlated with SPECT findings in three[83-85], and with xenon CT in one[86]. All found that MR perfusion techniques correlated well with the perfusion deficit demonstrated on these other modalities. Sample sizes were small and it was not made clear whether perfusion images were read blinded to other forms of imaging.

7.3.3 Studies of DWI and PI in combination

Identified studies and general methodological details

Nineteen studies were identified with a total sample size of 563 (median 21). The main purpose of three (197) was to document the clinicotopography of the combined imaging[87-89]. Sample sizes were small and it was not documented whether DWI and PI were read blinded to clinical details. One study (nine patients) compared DWI/PI to CT in the interpretation of haemorrhage, and again no details were given with regards blinding[90]. One study (41 patients) explored the clinical feasibility of DWI/PI[91]. Although the resulting data were encouraging on the speed of the process, they were lacking on patient clinical characteristics and importantly, the proportion of patients the imaged group represented in relation to the total number of patients with stroke symptoms presenting to the study hospital.

DWI/PI, final infarct size and clinical outcome

Fourteen studies (316 patients) were mainly concerned with the use of DWI/PI in predicting either the final size of infarct on conventional imaging[92-97] or final infarct size and clinical outcome[98-105]. The median sample size was 20 patients and four of these studies reported inclusion of patients from previously published papers. Follow-up imaging was performed between three and 277 (median eight) days after initial

scanning. Studies that used later time points did not make clear whether ex vacuo effects (potentially leading to an underestimation in infarct size[106], see discussion) were taken into account.

In the nine studies that related DWI/PI patterns to clinical outcome, follow-up ranged from one to 90 days after stroke. The scales used varied, the commonest being the NIHSS[92;98;99;102;103;105], which is a measure of neurological deficit not functional outcome. The size of lesion on acute DWI or PI correlated with final clinical outcome using both the NIHSS, the Canadian Neurological Scale (CNS)[100;101], and the European Stroke Scale (ESS)[104].

The DWI/PI 'mismatch'

Varying patterns of 'mismatch' between lesion extent on DWI and PI were seen and opinions given as to what these patterns represented. Where PI lesions were larger than DWI, investigators inferred a larger area of brain under threat of ischaemia that outlined by the DWI lesion, i.e. an ischaemic penumbra. Where DWI lesions were larger than PI lesions, or no associated PI lesion was visible, the investigators inferred that a degree of reperfusion had occurred but that an area of permanent damage, represented by the DWI lesion had already occurred. Where no DWI lesion was visible in the presence of a PI deficit, it was inferred that there was an arterial occlusion but no ischaemic damage at the time of imaging[101]. 11 studies (225 patients) used MR angiography (MRA) in their imaging protocols as well as PI and DWI, some of which helped to support the findings of PI by demonstrating an appropriately occluded artery[88;90;94;95;97;99-102;104;105], but otherwise there was no other objective way for substantiating the 'mismatch' theory. The proportion of patients in whom the lesion behaved as predicted on the follow-up imaging (i.e. where PI > DWI, the area of ischaemia on the follow-up scan increased in size) varied from 100% to only 56%.

7.3.4 Data from more recently published studies

Between October 1999 and April 2001, a search of MEDLINE and EMBASE revealed a further 102 studies published on DWI and PI. Of 52 studies that were reviewed, the median sample size was 27, scans were examined blinded to clinical history or imaging

in 17/52 (33%). Documenting the patterns seen in small samples remained the primary purpose in a large proportion of studies (44%). 14 studies explored technical issues such as the differences in ADC values between grey and white matter[107-109], or in lesions with haemorrhagic transformation[110]. Two studies commenting on the feasibility of DWI protocols documented significant numbers of exclusions[111;112]; one of which performed a DWI protocol in only about 10% of strokes presenting to their facility[112]. Further work was published on the significance of DWI/PI mismatches[113;114], but exactly what the mismatch represents remains unresolved. Three studies (197 patients) documented the superiority of DWI over conventional imaging in the demonstration of lesions[115-117].

7.4 Discussion

The importance of demonstrating clinical benefit with DWI/PI

Acutely ill patients are poor MRI subjects; they are restless, may be confused and unable to lie still for prolonged scan times, and observing their clinical state is difficult. Lying supine when the ability to protect the airway is impaired increases the risk of aspiration (roughly 50% of all strokes have impaired swallowing reflex acutely[118]). To justify their incorporation into patient care, DWI and PI have to genuinely provide information over and above that which is readily available on a plain CT, *and* this information should alter clinical management. The quality of any information gained should also outweigh any loss of treatment efficacy resulting from added time delay to start of treatment, an important criteria in this era of thrombolysis. Are the data available with which to start making such judgements?

Published studies are methodologically weak

The results of this systematic review show that publications in this field so far are repeating the mistakes of CT and conventional MRI, in that they tend not to include important methodological details. In many studies, the advanced imaging was not read blinded to the more routine imaging, there was little information on patients unable to complete DWI or PI, and most studies lacked clinical details of patient selection and case mix. No details were given on the order in which imaging was performed, and if

DWI was always performed after conventional imaging, as with studies so far that have compared conventional MRI to CT, it is likely therefore, that DWI would always show more lesions.

The data needed to determine the sensitivity and specificity of DWI for identifying acute ischaemic lesions and of DWI/PI for identifying salvageable tissue were not available. One important case series of patients with stroke but negative scans (taken from a series of over 700 patients) mentioned that specificity was not addressed[68]. Such a task would indeed have been a major undertaking, but it would give us information on sensitivity and specificity of DWI with an accuracy that smaller studies that have attempted to address this issue[57] have not achieved. Other studies have attempted to define specificity and sensitivity of DWI[61;44], but selection bias make it difficult to extrapolate these values to the general population with stroke-like symptoms.

Although it is likely that DWI is more sensitive to acute ischaemic stroke than conventional MRI or CT, the sample sizes were so small, and there were insufficient details of clinical features, inclusion and exclusion criteria, and unsuccessful examinations to make an accurate estimation of its merit compared to CT or conventional MRI to be made.

The importance of case-mix

Descriptions of case-mix in studies so far are scanty at best, and this is one of the main weaknesses of the existing data; case-mix is crucial for a number of reasons. Firstly, some conditions that mimic stroke clinically can also manifest abnormalities on DWI[27;119;120]. Few studies mentioned whether or not any of their prospectively identified patients later turned out not to have had a stroke, though it would be unusual, in a prospective sample even as small as 40, not to find the occasional patient thought initially to have had a stroke, to turn out to have a non-vascular cause of their symptoms[121]. Conversely, the study by Ay[68] and other case reports[122;123] have highlighted the potential for DWI to be negative in patients with ischaemic stroke. Although PI may be of some use in these patients, clarification around this issue is sorely needed.

Secondly, as stroke is a heterogeneous condition and the case mix of patients is likely to differ between hospitals (even within one small geographical area), this will have led to differences between studies in the type of stroke patients included. However, unless sufficient details of the patients' clinical characteristics at baseline (age, gender, some measure of neurological deficit, prestroke morbidity etc) and clinical status at a recognised, valid outcome point (e.g. three months), by a validated outcome score are given, it is impossible to gauge the generalisability of the individual study results, hence the relevance to the stroke population in general. One month after stroke is far too early to determine clinical outcome, and still too early for radiological outcome. There may still be either swelling (overestimating final infarct size[124]) or fogging (grossly underestimating final infarct size[125]). In fact, use of *any* radiological outcome is difficult if a volume measure or image co-registration are used because (in addition to swelling and fogging), loss of volume in the affected area and ex-vacuo effects in surrounding tissues from four to six weeks onwards[124] will lead to underestimation of final infarct volume.

Thirdly, the clinical severity of the stroke is a profound determinant of clinical outcome, correlating strongly with the site and extent of the lesion on CT and conventional MRI. Stroke severity must be taken into consideration before any additional information contributed by an imaging technique to the identification of particular patients, or the determination of outcome can be identified[126]. Most studies failed to do this adequately. Stroke severity also influences the time to admission to hospital (severe strokes are admitted sooner after stroke than milder ones[127]), and hence will influence the time to imaging. This in turn will probably influence the ADC values found in individual patients. Failure to take account of case-mix may have also contributed to perceived differences between studies that compared ADC changes over time where 'snapshots' of different patients at different times were used instead of the same patients scanned serially at different times. A similar effect most probably affects the findings in studies of DWI with PI where the proportion of patients with diffusion/perfusion mismatch and its size will depend on the severity of stroke included and the time delay to imaging.

The problem with small sample sizes

In all cases, the sample size was small. Also, our totals may overestimate the true number imaged, as some patients were included in several different publications. Small sample size makes the studies vulnerable to the play of chance in the mix of patients included and the study results. Examples of how profound an effect the play of chance can have, can be found in the systematic review of early trials of thrombolysis for acute myocardial infarction[128] (in which studies with sample sizes up to several hundreds had diametrically opposite results), and in an exercise to demonstrate the effect of chance on small sample sizes (DICE therapy - Don't Ignore Chance Effects)[129]. Investigators should be encouraged to combine their existing individual patient data from different individual studies, and participate in new multi-centre studies wherever possible, thereby achieving much larger sample sizes and over-coming some of the case mix problems outlined above. The numbers of patients required to obtain more robust data on the efficacy of DWI and/or PI in individual studies are not large however. Only 84 patients would be required to show (with 90% power) that DWI demonstrated lesions in 90%, as opposed to CT showing lesions in 60% of patients.

Unresolved technical issues

Although many studies gave ample details of the imaging sequences used, there are problems with the precise DWI or PI parameters to be measured, more so with PI. Most MR PI techniques measure relative not absolute perfusion changes and Positron Emission Tomography (PET) studies have demonstrated drawbacks with this approach[130]. Relative perfusion values may not precisely demonstrate which tissue is at greatest risk of infarction, added to which, is the unresolved debate about which is the best parameter of the PI curve to use in the analysis. Attempting to ascribe a physiological mechanism to PI findings on the basis of our current knowledge is to risk mistaking association for causation. Very detailed analysis of small datasets (e.g. 30 patients) may be used to generate hypotheses to test in new studies. However conclusions from such analysis are data-dependent in themselves, and placing too much reliance on the results might be misleading[131], particularly in the absence of any spontaneous or pharmacologically induced tissue recovery to identify what tissue really is salvageable. An example of this type of error about 10 years ago was the overemphasis of the association between haemorrhagic transformation and

cardioembolic stroke. Then, it was incorrectly assumed that cardioembolic stroke *caused* haemorrhagic transformation, because of an observed *association*, when in fact, it was the size of the infarct rather than the mechanism per se that was responsible[132;133]. The relevance of this is that investigators then used the presence of haemorrhagic transformation to diagnose cardioembolic stroke, when of course any arterial infarct may become haemorrhagic, as may venous infarction.

Mismatch equals penumbra – appealing theory based on what evidence?

Three of the studies that compared DWI/PI with final infarct size commented on the nature of the lesion visualized by DWI. Opinions varied; one study[92] implied that the DWI lesion was infarcted tissue, another stated that 'DWI lesions do not reflect closely the extent of functionally compromised tissue'[101], and another[93] stated that diffusion abnormalities indicated reversible and irreversible ischaemia. No studies used any other imaging methods to corroborate these theories therefore, it was not clear on what evidence these statements were based.

Do more recent studies resolve any of these issues?

In spite of the continuing interest in DWI and PI, as demonstrated by the high volume of publications since the original search, little has been resolved. Samples are still too small and highly selected. Studies are still commonly not blinded. There have been encouraging studies of the superiority of DWI in the demonstration of lesions compared to conventional imaging, but the majority concentrate on the first one or two days after stroke, which would inevitably limit its use. Encouraging work with SPECT is beginning to attempt to quantify viable ischaemic tissue[134], but we are barely any further forward in determining the physiological significance of the diffusion/perfusion mismatch.

Conclusion

DWI and PI may represent an exciting step forward in the management of stroke, but the studies using these techniques published so far do not contain the data necessary to determine their precise therapeutic impact. Before we can be sure they represent an

improvement over and above plain CT, we need to determine what it is these images depict with greater certainty, and get some measure of how much more clinically useful they are than conventional imaging, if that is indeed the case. Some of the issues raised above concerning the effect of stroke severity on ADC values (and visibility of lesions), and the clinical utility of DWI will be explored in further detail using our own data, in the next chapter.

Table 1. DWI only in the identification of stroke

Study	Date	N of patients	Purpose	Timing of scan (from symptom onset)	Readings blinded?	Results
Chien[31]	92	15	technical study (diffusion maps in ischaemia)	Undefined	No	
Warach[15]	92	32	early lesions (MRI), timing	6 groups ranging from <12hours to>4months	Yes	DWI showed lesions in 4 earliest scans (<4hrs) when MRI didn't. (12.5%)
de Crespigny[25]	95	20	technical study (navigator diffusion imaging)	Undefined	No	
Welch[30]	95	8	technical study (MRI tissue signature model)	24 to 116 hours	No	
Warach[41]	95	40	early lesions (MRI), timing	Undefined (for *all* patients included)	No	DWI showed lesions in 11/40 and MRI none; this subgroup all under 6 hrs, may be scans rather than whole patients. (28%)
Marks[19]	96	29	technical study (navigated spin echo imaging)	3 groups ranging from <16hours to>10days	No	
Bruning[49]	96	24	compare to MRI, feasibility	2 groups ranging from <12hours to <16weeks	No	3 vs 2 positive in first 12 hrs
Bartylla[27]	97	41	early lesions, new vs old	8 hrs - 12 days	No	DWI 38/41; MRI 30/41. (20%)
Okada[67]	97	29	haemorrhage	Undefined	No	
Lindgren[53]	97	15	new vs old	< 50 hrs	No	
Ulug[5]	97	6	technical study (quantifying ADC)	<24hours to >1year	No	
Ebisu[66]	97	25	haemorrhage	4 groups ranging from <3days to >31 days	No	
Lutsep[45]	97	103	early lesions	Mean of 10.4 days (range undefined)	No	DWI showed lesions in 8/103 cases not seen on MRI. (8%)
Lovblad[12]	97	50	outcome (NIHSS + BI)	< 24 hrs	Yes	
Schlaug[40]	97	157	timing (monitoring change in ADC)	24 hrs to over 30 days	No	
O'uchi[42]	98	224	timing, new vs old	< 22 days	No	
Burdette[39]	98	85	timing	<1day to >20days	No	

Study	Date	N of patients	Purpose	Timing of scan (from symptom onset)	Readings blinded?	Results
Nagesh[29]	98	9	technical study (heterogeneity of ADC)	< 10 hrs	No	
Singer[57]	98	39	early lesions, new vs old, specific subtype (subcortical)	<4/7	Yes	DWI 37/39; MRI (fse) 35/39. (5%)
Fitzek[51]	98	15	new vs old (MRI, CT)	<11/7	No	
Noguchi[56]	98	35	early lesions (MRI), subtype, clinicotopography	< 3/7	No	in <6hrs, DWI lesions seen in 3 where MRI was normal. (9%)
van Everdingen[17]	98	42	outcome (NIHSS, BI, Rankin)	< 60 hrs	Yes	
Chong[14]	98	26	technical study (postacquisition processing)	< 4/7	Yes	
Lovblad[61]	98	194	feasibility	< 24 hrs	No	
Inoue[50]	98	34	early lesions	< 8hrs	No	DWI 30/34; MRI 6/34. (71%)
Read[64]	98	9	feasibility, early lesions	3.75 hrs - 3/7	No	DWI 7/9; MRI 6/9; CT 2/9. (11%)
Lovblad[65]	98	32	feasibility, early lesions	1.5 - 47 hrs	No	in the < 6 hrs: DWI 10/32; 'conventional' 0/32. (31%)
Maier[26]	98	8	technical study (MR line diffusion imaging)	8 hours to 229 days	No	
Lovblad[24]	98	40	technical study (merits of HASTE imaging)	< 24 hrs	No	
Sorensen[32]	99	50	technical study	see sorensen 96	No	
Yang[21]	99	26	timing (monitoring change in ADC)	< 24, 3-5/7, 3 months (serial study)	No	
Engelter[60]	99	40	clinicotopography	< 24 hrs	No	
Gonzalez[44]	99	22	early lesions (MRI, CT)	<6hrs	No	DWI 14/14; CT 4/14. (71%)
Hakan[58]	99	62	clinicotopography	< 3/7	No	
Lovblad[62]	99	169	feasibility, technical study (single-shot MRI)	Undefined	No	
Ay[68]	99	27	outcome (negative DWIs)	<38 hrs, and FU 1-7 days	No	
Kumon[54]	99	140	clinical outcome	6 hours to 33 days	No	
Kidwell[59]	99	42	subtype (TIA), feasibility, clinicotopography	< 24 hrs	No	
Ricci[63]	99	72	technical study, feasibility	< 10/7	No	

Study	Date	N of patients	Purpose	Timing of scan (from symptom onset)	Readings blinded?	Results
Yamada[48]	99	29	early lesions (T1 MRI)	9 hrs - 27 days	No	can't tell
Barber[10]	99	17	early lesions (CT)	< 6 hrs	Yes	DWI 16/16; CT 12/16. (25%)
Schonewille[55]	99	43	subtype (lacunars), clinicotopography	< 6/7	Yes	
Altieri[52]	99	43	new vs old	< 15/7	No	
Geijer[16]	99	27	new vs old, (MRI), technical study	< 57 hrs (1< 12hrs)	Yes	
Bammer[36]	99	34	technical study (another alternative to EPI)	1.5 hrs - 34/7	No	
Provenzale[38]	99	21	technical study (exponential images)	2 groups ranging from>3days to <28days	No	
Burdette[35]	99	30	technical study (contibrution of shine through)	< 7/7	No	
Li[34]	99	3	technical study (ADC mapping)	Undefined	No	
Lansberg[69]	2000	19	Inter observer reliability (compared to CT)	<7hours, and FU 36 hours	Yes	DWI 100%; CT 42-63%
Albers[70]	2000	40	Clinical utility	<24hours	Yes	

Table 2. PI only studies

Study	Date	N of patients	Timing	Purpose
Edelman[7]	90	50	Undefined	Technical study (demonstrating CBF)
Warach[72]	92	34	< 48 hours	Technical study (analyse PI with MRA)
Guckel[75]	94	17	Undefined	Technical study (DSC method),
Sorensen[74]	95	5	3 to 91 weeks	Technical study (evaluate accuracy), feasibility
Hacklander[80]	96	9	3 groups; < 24 hours to > 7 days	Technical (measure CBF)
Rother[71]	96	15	< 6 hours	Feasibility, outcome (SSS)
Reith[77]	97	6	Undefined	Technical study (measured perfusion changes)
Wu[73]	97	11	3 groups < 48 hours; 5 to 15 days; 3 to 25 months	Technical study (measuring CBF)
Siewert[8]	97	18	3-2000 hours	Technical study (comparing contrast techniques)
Schreiber[81]	98	2	< 5 hours	Technical study (new method for mapping CBF)
Soher[78]	98	10	< 24 hours	Technical study (compare CBF to BAT)
Berthezene[76]	98	2	4 weeks	Technical study (effect of metabolic depression on CBF)
Yamada[82]	99	10	6 to 120 days	Technical study (crossed cerebellar diaschisis)
Nighoghossian[79]	99	9	> 2 weeks	Technical study (can PI demonstrate CBF?)

Table 3. DWI and PI in combination in ischaemic stroke

Study	Date	N of patients	Timing	Purpose	Proportion of patients with follow-up scans	Timing of follow-up scan
Warach[98]	96	19	Undefined	Outcome (NIHSS at scan & 1 week)	15/15 (who had both) (T2WI/CT)	Undefined
Sorensen[97]	96	11	< 10 hours	Compare to CT/MRI	11/11 (T2WI)	< 2 weeks
Baird[96]	97	28	< 60 hours	Correlate initial and final lesions	13/13 (who had PI)	<7 days
Flacke[89]	98	18	2 groups < 6hours, 6 to 48 hours	Feasibility, clinicotopography	Undefined	Undefined
Schwamm[99]	98	14	< 13 hours	Outcome (NIHSS before each scan)	13/14	>6 weeks
Barber[101]	98	18	3 groups ranging from < 24 hours to within 120 days	Outcome (CNS at acute & subacute; final BI & Rankin)	15/18	>3 weeks
Tong[105]	98	10	< 6.5 hours	Outcome (NIHSS at presentation & 24 hrs)	8/10 (T2WI)	<7 days
Rordorf[95]	98	17	<12 hours	Compare to final CT/MRI	17/17 (T2WI/CT)	<7 days
Wang[87]	98	145	Undefined	Clinicotopography	Undefined	Undefined
Ueda[93]	99	18	< 72 hours	Technical study, correlate to final lesion	15/18	>2 weeks
Karonen[92]	99	46	days 1, 2 and 8	Evaluate PWI/DWI mismatch, outcome (NIHSS)	33-39/46	<7 days
Barber[100]	99	26	13 groups ranging from 1 day to within 120 days	Outcome (CNS at acute & subacute. final CNS, BI, Rankin)	21/26	>3 months

Study	Date	N of patients	Timing	Purpose	Proportion of patients with follow-up scans	Timing of follow-up scan
Neumann-Haefelin[104]	99	30	1st. <24hrs, 2nd. 6-10/7	Evaluate PWI/DWI mismatch, outcome	20/30	<7/7
Beaulieu[103]	99	21	5 time points: 7 hrs to 30 days	Correlate lesions and outcome (NIHSS)	15/21	30/7
Darby[88]	99	34	< 24 hrs	Clinicotopography	0	
Sunshine[91]	99	41	< 6 hrs	Feasibility	0	
Jansen[102]	99	35	< 11.5 hours	Feasibility, outcome (NIHSS, SSS, BI, RI)	35/35	<5/7
Schellinger[90]	99	9	< 6 hrs	Feasibility	0	
Sorensen[94]	99	23	< 12 hrs	Compare to CT/MRI	23/26 (rest of lesions too small)	3-59/7 (median 6/7)

1. Mohr JP. Thrombolytic therapy for ischemic stroke: from clinical trials to clinical practice. JAMA 2000;283:1189-91.

2. Prichard JW,.Grossman RI. New reasons for early use of MRI in stroke. Neurology 1999;52:1733-6.

3. Hacke W,.Warach S. Diffusion-weighted MRI as an evolving standard of care in acute stroke. Neurology 2000;54:1548-9.

4. Provenzale JM,.Sorensen AG. Diffusion-weighted MR imaging in acute stroke: theoretic considerations and clinical applications. AJR 1999;173:1459-67.

5. Ulug AM, Beauchamp N, Jr., Bryan RN, van, Zijl PC. Absolute quantitation of diffusion constants in human stroke. Stroke 1997;28:483-90.

6. Mills R. Self-diffusion in normal and heavy water in the range 1 - 45 degrees. J Physical Chemistry 1973;77:685-8.

7. Edelman RR, Mattle HP, Atkinson DJ, Hill T, Finn JP, Mayman C. Cerebral blood flow: assessment with dynamic contrast-enhanced T2-weighted MR imaging at 1.5 T. Radiology 1990;176:211-20.

8. Siewert B, Schlaug G, Edelman RR, Warach S. Comparison of EPISTAR and T2*-weighted gadolinium-enhanced perfusion imaging in patients with acute cerebral ischemia. Neurology 1997;48:673-9.

9. Jarvik JG, Haynor DR, Longstreth WT, Jr. Assessing the usefulness of diagnostic tests. Am J Neuroradiol 1996;17:1255-8.

10. Barber PA, Darby DG, Desmond PM, Gerraty RP, Yang Q, Li T et al. Identification of major ischemic change: Diffusion-weighted imaging versus computed tomography. Stroke 1999;30:2059-65.

11. Lansberg MG, Albers GW, Beaulieu C, Marks MP. Comparison of diffusion-weighted MRI and CT in acute stroke. Neurology 2000;54:1557-61.

12. Lovblad KO, Baird AE, Schlaug G, Benfield A, Siewert B, Voetsch B et al. Ischemic lesion volumes in acute stroke by diffusion-weighted magnetic resonance imaging correlate with clinical outcome. Ann Neurol 1997;42:164-70.

13. Schonewille WJ, Tuhrim S, Singer MB, Atlas SW. Diffusion-weighted MRI in acute lacunar syndromes: A clinical- radiological correlation study. Stroke 1999;30:2066-9.

14. Chong J, Lu D, Aragao F, Singer MB, Schonewille WJ, Silvers A et al. Diffusion-weighted MR of acute cerebral infarction: comparison of data processing methods. Ajnr: American Journal of Neuroradiology 1998;19:1733-9.

15. Warach S, Chien D, Li W, Ronthal M, Edelman RR. Fast magnetic resonance diffusion-weighted imaging of acute human stroke. Neurology 1992;42:1717-23.

16. Geijer B, Brockstedt S, Lindgren A, Stahlberg F, Norrving B, Holtas S. Radiological diagnosis of acute stroke. Comparison of conventional MR imaging, echo-planar diffusion-weighted imaging, and spin-echo diffusion-weighted imaging. Acta Radiologica 1999;40:255-62.

17. van Everdingen KJ, van, der Grond J, Kappelle LJ, Ramos LM, Mali WP. Diffusion-weighted magnetic resonance imaging in acute stroke. Stroke 1998;29:1783-90.

18. Singer MB, Chong J, Lu D, Schonewille WJ, Tuhrim S, Atlas SW. Diffusion-weighted MRI in acute subcortical infarction. Stroke 1998;29:133-6.

19. Marks MP, de Crespigny A, Lentz D, Enzmann DR, Albers GW, Moseley ME. Acute and chronic stroke: navigated spin-echo diffusion-weighted MR imaging. Radiology 1996;199:403-8.

20. Lovblad KO, Laubach HJ, Baird AE, Curtin F, Schlaug G, Edelman RR et al. Clinical experience with diffusion-weighted MR in patients with acute stroke. Ajnr: American Journal of Neuroradiology 1998;19:1061-6.

21. Yang Q, Tress BM, Barber PA, Desmond PM, Darby DG, Gerraty RP et al. Serial study of apparent diffusion coefficient and anisotropy in patients with acute stroke. Stroke 1999;30:2382-90.

22. Wilcock DJ, Jones DK, Horsfield MA, Cherryman GR. Echoplanar MRI in patients with an acute stroke syndrome. British Journal of Radiology 1999;72:914-21.

23. Albers GW, Lansberg MG, Norbash AM, Tong DC, O'Brien MW, Woolfenden AR et al. Yield of diffusion-weighted MRI for detection of potentially relevant findings in stroke patients. Neurology 2000;54:1562-7.

24. Lovblad KO, Jakob PM, Chen Q, Baird AE, Schlaug G, Warach S et al. Turbo spin-echo diffusion-weighted MR of ischemic stroke. Ajnr: American Journal of Neuroradiology 1998;19:201-8.

25. de Crespigny AJ, Marks MP, Enzmann DR, Moseley ME. Navigated diffusion imaging of normal and ischemic human brain. Magnetic Resonance in Medicine 1995;33:720-8.

26. Maier SE, Gudbjartsson H, Patz S, Hsu L, Lovblad KO, Edelman RR et al. Line scan diffusion imaging: characterization in healthy subjects and stroke patients. AJR 1998;American Journal of:85-93.

27. Bartylla K, Hagen T, Globel H, Jost V, Schneider G. Diffusion-weighted magnetic resonance imaging for demonstration of cerebral infarcts. Radiologe 1997;37:859-64.

28. Lovblad KO, Remonda L, Heid O, Schneider J, Gonner F, Schroth G. Clinical single-shot diffusion-weighted MRI of the human brain on a short-bore medium-filed imager. Neuroradiology 1999;41:889-94.

29. Nagesh V, Welch KM, Windham JP, Patel S, Levine SR, Hearshen D et al. Time course of ADCw changes in ischemic stroke: beyond the human eye: [see comments]. Stroke 1998;29:1778-82.

30. Welch KMA, Windham RA, Knight RA, Nagesh V, Hugg JW, Jacobs M. A model to predict the histopathology of human stroke using diffusion and T2-weighted magnetic resonance imaging. Stroke 1995;26:1983-9.

31. Chien D, Kwong KK, Gress DR, Buonanno FS, Buxton RB, Rosen BR. MR diffusion imaging of cerebral infarction in humans. Am J Neuroradiol 1992;13:1097-102.

32. Sorensen AG, Wu O, Copen WA, Davis TL, Koroshetz WJ, Reese T et al. Human acute cerebral ischaemia: detection of changes in water diffusion anisotropy by using MR imaging. Radiology 1999;212:785-92.

33. Ricci PE, Burdette JH, Elster AD, Reboussin DM. A comparison of fast spin-echo, fluid-attenuated inversion-recovery, and diffusion-weighted MR imaging in the first 10 days after cerebral infarction. Ajnr: American Journal of Neuroradiology 1999;20:1535-42.

34. Li T-Q, Takahashi AM, Hindmarsh T, Moseley ME. ADC mapping by means of a single-shot spiral MRI technique with application in acute cerebral ischemia. Magnetic Resonance in Medicine 1999;41:143-7.

35. Burdette JH, Elster AD, Ricci PE. Acute cerebral infarction: Quantification of spin-density and T2 shine- through phenomena on diffusion-weighted MR images. Radiology 1999;212:333-9.

36. Bammer R, Stollberger R, Augustin M, Simbrunner J, Offenbacher H, Kooijman H et al. Diffusion-weighted imaging with navigated interleaved echo-planar imaging and a conventional gradient system. Radiology 1999;211:799-806.

37. Ulug AM, Beauchamp N, Jr., Bryan RN, van, Zijl PC. Absolute quantitation of diffusion constants in human stroke. Stroke 1997;28:483-90.

38. Provenzale JM, Engelter ST, Petrella JR, Smith JS, MacFall JR. Use of MR exponential diffusion-weighted images to eradicate T2 "shine-through" effect. AJR 1999;American Journal of:537-9.

39. Burdette JH, Ricci PE, Petitti N, Elster AD. Cerebral infarction: time course of signal intensity changes on diffusion-weighted MR images. AJR 1998;American Journal of:791-5.

40. Schlaug G, Siewert B, Benfield A, Edelman RR, Warach S. Time course of the apparent diffusion coefficient (ADC) abnormality in human stroke. Neurology 1997;49:113-9.

41. Warach S, Gaa J, Siewert B, Wielopolski P, Edelman RR. Acute human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging. Ann Neurol 1995;37:231-41.

42. O'Uchi T, Kuru Y, Honda S, Hayashi T, Yasuda R. Application of diffusion-weighted EPI to cerebrovascular disease. Rivista di Neuroradiologia 1998;11:241-2.

43. Read SJ, Jackson GD, Abbott DF, Syngeniotis A, Mitchell LA, Fitt GR et al. Experience with diffusion-weighted imaging in an acute stroke unit. Cerebrovasc Dis 1998;8:135-43.

44. Gonzalez RG, Schaefer PW, Buonanno FS, Schwamm LH, Budzik RF, Rordorf G et al. Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset. Radiology 1999;210:155-62.

45. Lutsep HL, Albers GW, DeCrespigny A, Kamat GN, Marks MP, Moseley ME. Clinical utility of diffusion-weighted magnetic resonance imaging in the assessment of ischemic stroke. Ann Neurol 1997;41:574-80.

46. Noguchi K, Nagayoshi T, Watanabe N, Kanazawa T, Toyoshima S, Morijiri M et al. Diffusion-weighted echo-planar MRI of lacunar infarcts. Neuroradiology 1998;40:448-51.

47. Lovblad KO, Weber J, Heid O, Mattle HP, Schroth G. Clinical and radiological patterns of human stroke as defined by echo- planar diffusion-weighted MR imaging. Rivista di Neuroradiologia 1998;11:227-30.

48. Yamada N, Imakita S, Sakuma T. Value of diffusion-weighted imaging and apparent diffusion coefficient in recent cerebral infarctions: a correlative study with contrast-enhanced T1-weighted imaging. Ajnr: American Journal of Neuroradiology 1999;20:193-8.

49. Bruning R, Wu RH, Deimling M, Porn U, Haberl RL, Reiser M. Diffusion measurements in the ischemic human brain with a steady- state sequence. Investigative Radiology 1996;31:709-15.

50. Inoue T, Shimizu H, Fujiwara S, Yoshimoto T, Tsukamoto T. [Diffusion-weighted MRI detectability of acute cerebral ischemia: comparison with eventual infarction]. No to Shinkei - Brain & Nerve 1998;50:555-60.

51. Fitzek C, Tintera J, Muller-Forell W, Urban P, Thomke F, Fitzek S et al. Differentiation of recent and old cerebral infarcts by diffusion- weighted MRI. Neuroradiology 1998;40:778-82.

52. Altieri M, Metz RJ, Muller C, Maeder P, Meuli R, Bogousslavsky J. Multiple brain infarcts: Clinical and neuroimaging patterns using diffusion-weighted magnetic resonance. Eur Neurol 1999;42:76-82.

53. Lindgren A, Geijer B, Brockstedt S, Staaf G, Stahlberg F. The use of diffusion-MRI to differentiate acute cerebral infarcts from chronic lesions. Cerebrovasc Dis 1997;7:60.

54. Kumon Y, Zenke K, Kusunoki K, Oka Y, Sadamoto K, Ohue S et al. Diagnostic use of isotropic diffusion-weighted MRI in patients with ischaemic stroke: detection of the lesion responsible for the clinical deficit. Neuroradiology 1999;41:777-84.

55. Schonewille WJ, Tuhrim S, Singer MB, Atlas SW. Diffusion-weighted MRI in acute lacunar syndromes: A clinical- radiological correlation study. Stroke 1999;30:2066-9.

56. Noguchi K, Nagayoshi T, Watanabe N, Kanazawa T, Toyoshima S, Morijiri M et al. Diffusion-weighted echo-planar MRI of lacunar infarcts. Neuroradiology 1998;40:448-51.

57. Singer MB, Chong J, Lu D, Schonewille WJ, Tuhrim S, Atlas SW. Diffusion-weighted MRI in acute subcortical infarction. Stroke 1998;29:133-6.

58. Hakan A, Oliviera-Filho J, Buonanno FS, Ezzeddine M, Schaefer PW, Rordorf G et al. Diffusion-weighted imaging identifies a subset of lacunar infarction associated with embolic source. Stroke 1999;30:2644-50.

59. Kidwell CS, Alger JR, Di Salle F, Starkman S, Villablanca P, Bentson J et al. Diffusion MRI in patients with transient ischemic attacks. Stroke 1999;30:1174-80.

60. Engelter ST, Provenzale JM, Petrella JR, Alberts MJ. Diffusion MR imaging and Transient Ischaemic Attacks. Stroke 1999;30:2762-3.

61. Lovblad KO, Laubach HJ, Baird AE, Curtin F, Schlaug G, Edelman RR et al. Clinical experience with diffusion-weighted MR in patients with acute stroke. Ajnr: American Journal of Neuroradiology 1998;19:1061-6.

62. Lovblad KO, Remonda L, Heid O, Schneider J, Gonner F, Schroth G. Clinical single-shot diffusion-weighted MRI of the human brain on a short-bore medium-filed imager. Neuroradiology 1999;41:889-94.

63. Ricci PE, Burdette JH, Elster AD, Reboussin DM. A comparison of fast spin-echo, fluid-attenuated inversion-recovery, and diffusion-weighted MR imaging in the first 10 days after cerebral infarction. Ajnr: American Journal of Neuroradiology 1999;20:1535-42.

64. Read SJ, Jackson GD, Abbott DF, Syngeniotis A, Mitchell LA, Fitt GR et al. Experience with diffusion-weighted imaging in an acute stroke unit. Cerebrovasc Dis 1998;8:135-43.

65. Lovblad KO, Weber J, Heid O, Mattle HP, Schroth G. Clinical and radiological patterns of human stroke as defined by echo- planar diffusion-weighted MR imaging. Rivista di Neuroradiologia 1998;11:227-30.

66. Ebisu T, Tanaka C, Umeda M, Kitamura M, Fukunaga M, Aoki I et al. Hemorrhagic and nonhemorrhagic stroke: diagnosis with diffusion- weighted and T2-weighted echo-planar MR imaging. Radiology 1997;203:823-8.

67. Okada S, Cho K, Hosaka S, Ito K, Tajima N, Kobayashi S et al. Diffusion weighted EPI in early cerebral infarction and intracerebral hemorrhage. Japanese Journal of Clinical Radiology 1997;42:1519-25.

68. Ay H, Buonanno FS, Rordorf G, Schaefer PW, Schwamm LH, Wu O et al. Normal diffusion-weighted MRI during stroke-like deficits. Neurology 1999;52:1784-92.

69. Lansberg MG, Albers GW, Beaulieu C, Marks MP. Comparison of diffusion-weighted MRI and CT in acute stroke. Neurology 2000;54:1557-61.

70. Albers GW, Lansberg MG, Norbash AM, Tong DC, O'Brien MW, Woolfenden AR et al. Yield of diffusion-weighted MRI for detection of potentially relevant findings in stroke patients. Neurology 2000;54:1562-7.

71. Rother J, Guckel F, Neff W, Schwartz A, Hennerici M. Assessment of regional cerebral blood volume in acute human stroke by use of single-slice dynamic susceptibility contrast- enhanced magnetic resonance imaging. Stroke 1996;27:1088-93.

72. Warach S, Li W, Ronthal M, Edelman RR. Acute cerebral ischaemia:evaluation with dynamic contrast-enhanced MR imaging and MR angiography. Radiology 1992;182:41-7.

73. Wu RH, Bruening R, Berchtenbreiter C, Weber J, Steiger HJ, Peller M et al. MRI assessment of cerebral blood volume in patients with brain infarcts. Neuroradiology 1998;40:496-502.

74. Sorensen AG, Wray SH, Weisskoff RM, Boxerman JL, Davis TL, Caramia F et al. Functional MR of brain activity and perfusion in patients with chronic cortical stroke. Am J Neuroradiol 1995;16:1753-62.

75. Guckel F, Brix G, Rempp K, Deimling M, Rother J, Georgi M. Assessment of cerebral blood volume with dynamic susceptibility contrast enhanced gradient-echo imaging. J Comput Assist Tomography 1994;18:344-51.

76. Berthezene Y, Nighoghossian N, Damien J, Derex L, Trouillas P, Froment et al. Effects of thalamic hemorrhage on cortical hemodynamic parameters assessed by perfusion MR imaging: preliminary report. Journal of the Neurological Sciences 1998;157:67-72.

77. Reith W, Heiland S, Erb G, Benner T, Forsting M, Sartor K. Dynamic contrast-enhanced T2*-weighted MRI in patients with cerebrovascular disease. Neuroradiology 1997;39:250-7.

78. Soher BJ, Gillard JH, Bryan RN, Oppenheimer SM, Barker PB. Magnetic resonance perfusion imaging in acute middle cerebral artery stroke: comparison of blood volume and bolus peak arrival time. J Stroke Cerebrovasc Dis 1998;7:17-33.

79. Nighoghossian N, Berthezene Y, Adeleine P, Wiart M, Damien J, Derex L et al. Effects of subcortical cerebrovascular lesions on cortical hemodynamic parameters assessed by perfusion magnetic resonance imaging. Cerebrovasc Dis 1999; 9:136-41.

80. Hacklander T, Hofer M, Reichenbach JR, Rascher K, Furst G, Modder U. Cerebral blood volume maps with dynamic contrast-enhanced T1-weighted FLASH imaging: normal values and preliminary clinical results. J Comput Assist Tomography 1996;20:532-9.

81. Schreiber WG, Guckel F, Stritzke P, Schmiedek P, Schwartz A, Brix G. Cerebral blood flow and cerebrovascular reserve capacity: estimation by dynamic magnetic resonance imaging. Journal of Cerebral Blood Flow & Metabolism 1998;18:1143-56.

82. Yamada H, Koshimoto Y, Sadato N, Kawashima Y, Tanaka M, Tsuchida C et al. Crossed cerebellar diaschisis: Assessment with dynamic susceptibility contrast MR imaging. Radiology 1999;210:558-62.

83. Tsuchida C, Yamada H, Maeda M, Sadato N, Matsuda T, Kawamura Y et al. Evaluation of peri-infarcted hypoperfusion with T2*-weighted dynamic MRI. JMRI 1997;7:518-22.

84. Hatazawa J, Shimosegawa E, Toyoshima H, Ardekani BA, Suzuki A, Okudera et al. Cerebral blood volume in acute brain infarction: A combined study with dynamic susceptibility contrast MRI and 99mTc-HMPAO- SPECT. Stroke 1999;30:800-6.

85. Kim J, Shin T, Park J, Chung S, Choi N, Lim B. Various patterns of perfusion-weighted MR imaging and MR angiographic findings in hyperacute ischaemic stroke. Am J Neuroradiol 1999;20:613-20.

86. Hagen T, Bartylla K, Piepgras U. Correlation of regional cerebral blood flow measured by stable xenon CT and perfusion MRI. J Comput Assist Tomography 1999;23:257-64.

87. Wang AM, Shetty AN, Woo H, Rao SK, Manzione JV, Moore JR. Diffusion weighted MR imaging in evaluation of CNS disease. Rivista di Neuroradiologia 1998;11:109-12.

88. Darby DG, Barber PA, Gerraty RP, Desmond PM, Yang Q, Parsons M et al. Pathophysiological topography of acute ischemia by combined diffusion- weighted and perfusion MRI. Stroke 1999;30:2043-52.

89. Flacke S, Keller E, Hartmann A, Murtz P, Textor J, Urbach H et al. Improved diagnosis of early cerebral infarct by the combined use of diffusion and perfusion imaging. Rofo 1998;Fortschritte auf dem:493-501.

90. Schellinger PD, Jansen O, Fiebach JB, Hacke W, Sartor K. A standardized MRI stroke protocol: comparison with CT in hyperacute intracerebral hemorrhage. Stroke 1999;30:765-8.

91. Sunshine JL, Tarr RW, Lanzieri CF, Landis DMD, Selman WR, Lewin JS. Hyperacute stroke: Ultrafast MR imaging to triage patients prior to therapy. Radiology 1999;212:325-32.

92. Karonen JO, Vanninen RL, Liu Y, Ostergaard L, Kuikka JT. Combined diffusion and perfusion MRI with correlation to single-photon emission CT in acute ischaemic stroke. Stroke 1999;30:1583-90.

93. Ueda T, Yuh WTC, Maley JE, Quets JP, Hahn PY, Magnotta VA. Outcome of acute lesions evaluated by diffusion and perfusion MR imaging. Am J Neuroradiol 1999;20:983-9.

94. Sorensen AG, Copen WA, Ostergaard L, Buonanno FS, Gonzalez RG, Rordorf G et al. Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow, and mean tissue transit time. Radiology 1999;210:519-27.

95. Rordorf G, Koroshetz WJ, Copen WA, Cramer SC, Schaefer PW, Budzik RF. Regional ischaemia and ischemic injury in patients with acute middle cerebral artery stroke as defined by early diffusion-weighted and perfusion-weighted imaging. Stroke 1998;29:939-43.

96. Baird AE, Benfield A, Schlaug G, Siewert B, Lovblad KO, Edelman RR. Enlargement of human cerebral ischemic lesion volumes measured by diffusion-weighted magnetic resonance imaging. Ann Neurol 1997;41:581-9.

97. Sorensen GA, Buonanno FS, Gonzalez RG, Schwamm LH, Lev MH, Huang-Hellinger FR. Hyperacute stroke: evaluation with combined multisection diffusion-weighted and hemodynamically weighted echo-planar MR imaging. Radiology 1996;199:391-401.

98. Warach S, Dashe JF, Edelman RR. Clinical outcome in ischaemic stroke predicted by early diffusion-weighted and perfusion magnetic resonance imaging: a preliminary analysis. Journal of Cerebral Blood Flow & Metabolism 1996;16:53-9.

99. Schwamm LH, Koroshetz WJ, Sorensen G, Wang B, Copen WA. Time course of lesion developoment in patients with acute stroke. Serial diffusion- and hemodynamic-weighted magnetic resonance imaging. Stroke 1998;29:2268-76.

100. Barber PA, Davis SM, Darby DG, Desmond PM, Gerraty RP, Yang Q et al. Absent middle cerebral artery flow predicts the presence and evolution of the ischemic penumbra. Neurology 1999;52:1125-32.

101. Barber PA, Darby DG, Desmond PM, Yang Q, Gerraty RP, Jolley D. Prediction of stroke outcome with echoplanar perfusion- and diffusion-weighted MRI. Neurology 1998;51:418-26.

102. Jansen O, Schellinger PD, Fiebach JB, Hacke W, Sartor K. Early recanalisation in acute ischaemic stroke saves tissue at risk defined by MRI. Lancet 1999;353:2036-7.

103. Beaulieu C, de Crespigny A, Tong DC, Moseley ME, Albers GW, Marks MP. Longitudinal magnetic resonance imaging study of perfusion and diffusion in stroke: Evolution of lesion volume and correlation with clinical outcome. Ann Neurol 1999;46:568-78.

104. Neumann-Haefelin T, Wittsack H-J, Wenserski F, Siebler M, Seitz RJ. Diffusion- and perfusion-weighted MRI. The DWI/PWI mismatch region in acute stroke. Stroke 1999;30:1591-7.

105. Tong DC, Yenari MA, Albers GW, O'Brien M, Marks MP, Moseley ME. Correlation of perfusion- and diffusion-weighted MRI with NIHSS score in acute (<6.5 hour) ischemic stroke [see comments]. Neurology 1998;50:864-70.

106. Wardlaw JM. What pathological type of stroke is it? (first edition). In Warlow CP, Dennis MS, Hankey GJ, Sandercock PAG, van Gijn J, Wardlaw JM, eds. Stroke: a practical guide to management , pp 146-89. Oxford: Blackwell Scientific Ltd, 1996.

107. Bastin ME, Rana AK, Wardlaw JM, Armitage PA, Keir SL. A study of apparent diffusion coefficient of grey and white matter in human ischaemic stroke. Neuroreport 2000;11:2867-74.

108. Doege CA, Kerskens CM, Romero BI, Brunecker P, Junge H, ller B et al. MRI of small human stroke shows reversible diffusion changes in subcortical gray matter. Neuroreport 2000;11:2021-4.

109. Mukherjee P, Bahn MM, McKinstry RC, Shimony JS, Cull TS, Akbudak E et al. Differences between gray matter and white matter water diffusion in stroke: Diffusion-tensor MR imaging in 12 patients. Radiology 2000;215:211-20.

110. Tong DC, Adami A, Moseley ME, Marks MP. Relationship between apparent diffusion coefficient and subsequent hemorrhagic transformation following acute ischemic stroke. Stroke (Online) 2000;31:2378-84.

111. Oppenheim C, Logak M, Dormont D, Ricy S et al. Diagnosis of acute ischaemic stroke with fluid-attenuated inversion recovery and diffusion-weighted sequences. Neuroradiology 2000;42:602-7.

112. Schellinger PD, Jansen O, Fiebach JB, Pohlers O, Ryssel H, Heiland et al. Feasibility and practicality of MR imaging of stroke in the management of hyperacute cerebral ischemia. [see comments]. Ajnr: American Journal of Neuroradiology 2000;21:1184-9.

113. Ezura M, Takahashi A, Shimizu H, Yoshimoto T. Diffusion-weighted MRI and selection of patients for fibrinolytic therapy of acute cerebral ischaemia. Neuroradiology 2000;42:379-83.

114. Karonen JO, Liu Y, Vanninen RL, Ostergaard L, Kaarina Partanen PL, Vainio PA et al. Combined perfusion- and diffusion-weighted MR imaging in acute ischemic stroke during the 1st week: a longitudinal study. Radiology 2000;217:886-94.

115. Urbach H, Flacke S, Keller E, Textor J, Berlis A, Hartmann A et al. Detectability and detection rate of acute cerebral hemisphere infarcts on CT and diffusion-weighted MRI. Neuroradiology 2000;42:722-7.

116. Rovira A, Pedraza S, Molina C, Capellades J, Grive E, Rovira A et al. Diffusion-weighted magnetic resonance in the diagnosis of acute subcortical infarcts. Revista de Neurologia 2000;30:914-9.

117. Oliveira-Filho J, Ay H, Schaefer PW, Buonanno FS, Chang Y, Gonzalez et al. Diffusion-weighted magnetic resonance imaging identifies the "clinically relevant" small-penetrator infarcts. Archives of Neurology 2000;57:1009-14.

118. Smithard DG, O'Neill PA, Parks C, Morris J. Complications and outcome after acute stroke. Does dysphagia matter? Stroke 1996;27:1200-4.

119. Lansberg MG, O'Brien MW, Norbash AM, Moseley ME, Morrell M, Albers GW. MRI abnormalities associated with partial status epilepticus. Neurology 1999;52:1021-7.

120. Lim CC, Sitoh YY, Lee KE, Kurup A, Hui F. Meningoencephalitis caused by a novel paramyxovirus: an advanced MRI case report in an emerging disease. Singapore Med.J. 1999;40:356-8.

121. Libman RB, Wirkowski E, Alvir J, Rao TH. Conditions that mimic stroke in the emergency department. Implications for acute stroke trials. Archives of Neurology 1995;52:1119-22.

122. Lefkowitz D, LaBenz M, Nudo SR, Steg RE, Bertoni JM. Hyperacute ischaemic stroke missed by diffusion-weighted imaging. Am J Neuroradiol 2000;20:1871-5.

123. Wang PY, Barker PB, Wityk RJ, Ulug AM. Diffusion-negative stroke: a report of two cases. Am J Neuroradiol 1999;20:1876-80.

124. Wardlaw JM. What pathological type of stroke is it? (first edition). In Warlow CP, Dennis MS, Hankey GJ, Sandercock PAG, van Gijn J, Wardlaw JM, eds. Stroke: a practical guide to management , pp 146-89. Oxford: Blackwell Scientific Ltd, 1996.

125. Pereira AC, Doyle VL, Griffiths JR, Brown MM. Disappearing cerebral infarcts: a longitudinal MRI study of 16 patients. Cerebrovasc Dis 1997;7:30.

126. Wardlaw JM, Lewis SC, Dennis MS, Counsell C, McDowall M. Is visible infarction on computed tomography associated with an adverse prognosis in acute ischemic stroke? Stroke 1998;29:1315-9.

127. Uchino K,.Cramer S. Criteria and baseline characteristics predict outcome in acute stroke trials. Stroke 2000;31:277.

128. Yusuf S, Collins R, Peto R, Furburg C, Stampfer MJ, Goldhaber SZ. Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: Overview of results on mortality, reinfarction and side effects from 33 randomised controlled trials. Eur J Cardiol 1985;6:556-85.

129. Counsell C, Clarke MJ, Slattery J, Sandercock PAG. The miracle of DICE for acute stroke therapy: fact or fictional product of subgroup analysis? BMJ 1994;309:1677-81.

130. Powers WJ, Grubb RL, Jr., Raichle ME. Physiological responses to focal cerebral ischemia in humans. Ann.Neurol. 1984;16:546-52.

131. Marchal G, Benali K, Iglesias S, Viader F, Derlon JM, Baron JC. Voxel-based mapping of irreversible ischaemic damage with PET in acute stroke. Brain 1999;122 (Pt 12):2387-400.

132. Lodder J, Krijne-Kubat B, Broekman J. Cerebral hemorrhagic infarction at autopsy: cardiac embolic cause and the relationship to the cause of death. Stroke 1986;17:626-9.

133. Lodder J. CT detected haemorrhagic infarction: relation with size of infarct and the presence of midline shift. Acta Neurol Scand 1984;70:329-35.

134. Karonen JO, Vanninen RL, Liu Y, Ostergaard L, Kuikka JT. Combined diffusion and perfusion MRI with correlation to single-photon emission CT in acute ischaemic stroke. Stroke 1999;30:1583-90.

135. Barber PA, Darby DG, Desmond PM, Yang Q, Gerraty RP, Jolley D. Prediction of stroke outcome with echoplanar perfusion- and diffusion-weighted MRI. Neurology 1998;51:418-26.

136. Ueda T, Yuh WTC, Maley JE, Quets JP, Hahn PY, Magnotta VA. Outcome of acute lesions evaluated by diffusion and perfusion MR imaging. Am J Neuroradiol 1999;20:983-9.

137. Liu Y, Karonen JO, Vanninen RL, Ostergaard L, Roivainen R, Nuutinen et al. Cerebral hemodynamics in human acute ischemic stroke: a study with diffusion- and perfusion-weighted magnetic resonance imaging and SPECT. Journal of Cerebral Blood Flow & Metabolism 2000;20:910-20.

8 Diffusion-Weighted Magnetic Resonance Imaging In Stroke - Exploratory Analyses From Our Observational Case Series

8.1 Introduction

What do we need to know about diffusion-weighted imaging?

Although the quality of studies published so far on diffusion-weighted imaging (DWI) is not ideal, it is likely that DWI *can* demonstrate acute ischaemic stroke more frequently than computed tomography (CT)[1,2] or conventional magnetic resonance imaging (MRI)[3,4] and is likely to represent an exciting step forward in stroke imaging. However, questions remain over precisely how superior DWI is to conventional imaging, and in which patients it is most clinically useful. For instance, DWI can demonstrate lesions very early after stroke onset, but so too can CT and T2 MRI, especially in patients with clinically more severe strokes with larger lesions[5,6], who tend to present to hospital early[7]. It is not clear that DWI is more sensitive than conventional imaging in these hyperacute patients[8]. In fact, undue attention on using DWI in hyperacute stroke may have overlooked other important clinical uses of DWI in stroke. DWI may actually be more useful in milder strokes because of its ability to detect very small lesions better than conventional imaging[9,10]. Small lesions can be difficult to visualise using CT or conventional structural MRI [11,12].

There are a number of settings when making a positive diagnosis of, or confidently excluding, an ischaemic stroke would be clinically useful. For example, in a patient with prior stroke and further weakness (deterioration could be due to a further stroke or an intercurrent illness); if there was a suspicion of an unwitnessed seizure; or if it was unclear whether symptoms were due to a single occluded vessel or multiple emboli.

The need to quantify ischaemic damage in stroke - a role for DWI?

The changes due to ischaemic damage demonstrated on DWI can be quantified by calculating the apparent diffusion coefficient (ADC)[13] and measuring the volume of the

visible lesion. These variables may provide an objective assessment of tissue damage and this could be the ideal outcome predictors if they added predictive information beyond that obtained from baseline clinical examination alone, and the relationship with functional outcome were well characterised.

There have been several studies suggesting that the ADC and/or DWI lesion volume can predict outcome, i.e. the more abnormal the ADC, or the larger the visible lesion on DWI, the more severe the stroke and the worse the outcome.[14-18]. One study went so far as to suggest a cut off value for ADC of 0.56, below which outcome was poor[19,20]. However, the studies were small and did not specifically test for an *independent* association of imaging parameters with outcome, i.e. they did not test the extra predictive value of imaging over and above other prognostic factors.

The aims of our observational case series

We therefore set out to accumulate a prospective case series, with different stroke severities and outcomes, large enough to test the questions: 'in which clinical group of patients with stroke is visualising the responsible lesion with DWI of most use?' (the 'utility of DWI' study), and 'do DWI parameters such as ADC and DWI volume add independent prognostic information over and above clinical outcome predictors alone?' ('DWI and stroke severity' study).

8.2 Methods

Patient recruitment

As many patients as possible with acute ischaemic stroke admitted to our institution were recruited consecutively between February 1996 and August 1999. Inclusion criteria for this study were as follows: (i) well-defined onset of stroke symptoms; (ii) absence of cerebral haemorrhage or other non-vascular abnormality on CT or conventional MRI; (iii) no contraindications to MRI; (iv) subjects deemed able to tolerate the imaging protocol; (v) and the availability of the research MR scanner. Mild and severe strokes were included, and anterior as well as posterior circulation strokes.

No subjects received any investigational drugs. The study was approved by the local Ethics Committee.

Patients were examined by myself and categorised according to the Oxfordshire Community Stroke Project (OCSP) classification, and Canadian Neurological Scale (CNS) (appendices I and V) as soon as possible after admission, and prior to scanning.

At six months after stroke, patients were followed up by telephone or postal questionnaire by an operator who was blinded to the baseline clinical and imaging results. The patient's functional status was classified according to the modified Rankin scale (a global outcome measure with a 0 to 6 point scale: 0 indicating no symptoms, 5 indicating severe disability and 6 indicating dead, appendix IX)[21].

Imaging acquisition

Patients were scanned as soon as possible after admission. During the course of the study, the access to MRI changed so that the first 40 subjects were imaged on a 1.5 T Siemens Magnetom SP scanner, the next 68 subjects on an Elscint 2T Prestige scanner, and the remaining 45 subjects using a GE 1.5T Signa Horizon LX scanner. Both patient groups had routine structural imaging (T1-weighted, T2-weighted and proton density, see chapter 5 for parameters and appendix IV for glossary of terms) followed by DWI. Patients were scanned as soon as possible after admission or on the day of their outpatient clinic visit. Total scanning times were longer in the Siemens (non-echoplanar, about 45 minutes), and shorter on the Elscint and GE systems (echoplanar, 15 minutes).

Diffusion-weighted images were obtained on the Siemens scanner using a modified double spin echo sequence, which acquired an image echo (TE = 121 ms) and then a non-phase encoded navigator echo (TE = 152 ms). Before the image echo, two symmetric diffusion sensitising gradient pulses of magnitude zero (baseline) and 9.64 mT m^{-1} were applied sequentially along the read, phase encode and slice-select directions. The diffusion gradients were of duration 51 ms, and separation 57.4 ms, giving scalar b-values of approximately 0 and 700 s mm^{-2}. Motion artefacts arising from

bulk patient motion were corrected using the navigator echo data[22]. Other image acquisition parameters were as follows: 8 non-oblique axial slices, 1 NEX for both baseline and diffusion-weighted images, 5 mm slice thickness, 128 × 128 image matrix and a 230 × 230 mm field of view.

On the Elscint scanner, diffusion-weighted images were obtained using a single shot, half-Fourier, echo-planar imaging sequence, in which two symmetric diffusion sensitising gradient pulses of magnitude 0 (baseline) and 14 mT m^{-1}, duration of 40 ms and separation of 43.9 ms were applied sequentially in the read, phase-encode, and slice-select directions. Scalar b-values for this sequence (approximately 0 and 700 s mm^{-2}) were calculated numerically[23]. Other image acquisition parameters were as follows: 10 non-oblique axial slices, 1 NEX for both baseline and diffusion-weighted images, 6 mm slice thickness, 128 × 72 half-Fourier image matrix (zero filled to 256 × 128), 44 × 22 cm field of view, TR of 1 s per image and TE of 103 ms.

On the GE scanner, two diffusion sensitising gradient pulses of duration 32.2 ms with a separation of 30.09 ms were applied in six directions. Scalar b values were 0 and 1000 s mm^{-2}. 10 axial or axial-oblique slices of 5mm slice thickness were acquired, the image matrix was 128 x 128 and the field of view was 230 x 230 mm.

Image Analysis

The utility of DWI

A neuroradiologist examined the printed films of T2-weighted (T2-WI) and diffusion-weighted images on separate occasions, blinded to patient details and other imaging results. Scans were classified according to whether they demonstrated a recent infarction, a definite old infarct, or some other non-vascular lesion, or showed no lesion. 'Recent infarcts' were defined as an area of hyperintensitiy on DWI or on T2-WI in a distribution consistent with known vascular patterns. On T2-WI new was distinguished from old by the greater mass effect and less marked hyperintensity of the former than the latter.

Thereafter, the T2-WI and DWI results were combined, and DWI scans rated for 'clinical influence'. DWI scans were rated as 'helpful' if they distinguished a new from an old infarct, or identified a new infarct not visible on T2-WI. They were rated 'unhelpful' if recent infarction was visible on both DWI and T2-WI, or DWI did not demonstrate a recent lesion, or scans were technically of poor quality.

Having a DWI scan which demonstrated no lesion could also be of value to the clinician in making an appropriate diagnosis. Therefore, DWI scans were then reclassified as 'helpful' if they showed a definite new lesion not visible on T2-WI, or distinguished new from old infarct, or if they definitely showed no new lesion. They were reclassified as 'unhelpful' if the recent infarct was clearly visible on T2-WI or the DWI scan was technically poor, and so uninterpretable.

DWI and severity

A neuroradiologist examined the printed films of T2-WI and diffusion-weighted images on separate occasions, blind to patient details and all other imaging results. Scans were classified according to whether on T2-WI an infarct was not visible, faintly visible (slight hyper-intensity) or obvious (definite distinct hyperintensity) and whether the lesion was visible or not on the diffusion-weighted images. The T2-WI and DWI results were then compared and a rank order of visibility of lesions produced, according to whether the lesions were: (1) not visible on either T2-WI or DWI, (2) visible only on DWI, (3) faintly visible on T2-WI and clearly visible on DWI, and (4) clearly visible on T2-WI and DWI.

Images were processed off-line on a Sun Ultra Sparc Station 1 (Sun Microsystems, Mountain View, CA, USA). Baseline and diffusion-weighted images were aligned using SPM95 (http://www.fil.ion.ucl.ac.uk/spm) to correct for bulk patient movement between scans. Within each voxel the three orthogonal ADC components (ADC_x, ADC_y and ADC_z), were estimated by linear regression from the measured baseline and diffusion-weighted signal intensities. To avoid diffusion anisotropy effects[24], these three orthogonal ADC components were averaged to produce the apparent diffusion tensor

trace (ADC). The three component diffusion-weighted images were also averaged together to give average DWI maps. Maps of ADC were generated on a voxel-by-voxel basis and converted into Analyze (Mayo Foundation, Rochester, MN, USA) format. In patients with a hyper-intense lesion visible consistent with ischaemia, these regions were outlined on the ADC maps by a neuroradiologist blinded to all clinical and other imaging data. A mirror image area in the contralateral (normal) hemisphere was also outlined. For each slice, values of ADC for the lesion and mirror (contralateral) normal tissue regions were measured. Overall mean ADC values for the entire hyperintense lesion (and control) volumes were then calculated from these data. A ratio of the mean ADC for the lesion volume to the mean ADC of the normal (mirror image) brain volume was calculated (ADCr = ADC[ischaemic lesion]/ADC[normal]), so that each patient acted as their own control, and any effect of using different MRI scanners for the project was minimised.

Statistical analysis

The baseline clinical data, the imaging data and the functional outcome data were entered into a database, and analysed using the Statistical Package for Social Sciences (SPSS). For the utility of DWI study, the proportions of scans demonstrating recent infarction were compared using McNemar's test for matched data. The 'influence' of DWI was compared across OCSP stroke subtypes using a chi-squared analysis, and with the CNS using the non-parametric Mann-Whitney test. Odds ratios with 95% confidence intervals were also calculated.

In the DWI and stroke severity study, we examined the relationships between ADCr and imaging parameters (lesion volume on the ADC maps and infarct visibility on T2-WI/DWI), clinical features (initial stroke severity - OCSP classification and CNS), and six-month functional outcome. The non-parametric Kruskal Wallis test was used to compare: groups defined by their OCSP classification with timing of scanning, ADCr and lesion volume; and groups defined by how visible lesions were on T2-WI with Canadian Neurological Scale values and ADCr. The Mann Whitney U-test was used to compare functional outcome (dichotomised as dead or dependent or independent on

the modified Rankin scale, i.e. three to six versus zero to two respectively) with ADCr and lesion volume. Spearman's coefficient of correlation was used to compare: CNS values with timing of scanning, ADCr, lesion volume; and ADCr and lesion volume. As this was an exploratory analysis, we felt it was justifiable to examine multiple potential associations between clinical and imaging variables and outcome. We then performed a multiple logistic regression analysis to determine whether the ADCr was an independent predictor of outcome, over and above the initial clinical severity of the stroke (as determined by CNS) and the age of the patient. Only three variables were used in this exploratory analysis as there were too few patients and outcome events to build a more complex model[25].

8.3 Results

The analysis of the influence of stroke severity on DWI imaging parameters was performed using a database of 108 patients scanned using the Siemens and Elscint scanners. This group also formed the core of the analysis of the utility of DWI, to which a further 45 patients scanned on the GE Signa machine were added. Each study's baseline characteristics and results are described separately.

8.3.1 The utility of DWI

Patient baseline characteristics

153 subjects were scanned, 148 of which presented with stroke, five with transient ischaemic attack (TIA). The mean age was 67.6 years (range 19 to 93 years). The median time to scanning was two days and mean time to scanning was six days (range less than one to 77 days, in an outpatient), 102 (67%) were scanned within three days. The remaining 33% of patients were scanned at later times because they had presented late to hospital as outpatients. The median CNS was 8.5 (range 1.5 to 10) (table 1). In two patients, DWI scans were technically poor and completely uninterpretable. In patients presenting with a stroke, 13 (8.5% of total scanned) had total anterior circulation syndromes (TACS); 71 (46.4%) had partial anterior circulation syndromes

(PACS), 42 (27.5%) had lacunar syndromes (LACS); and 22 (14.4%) had posterior circulation syndromes (POCS).

Imaging findings

A greater proportion of DWI scans (107, 70%) demonstrated a relevant recent ischaemic lesion than did T2-WI (49, 32.0%), $p < 0.001$, (figure 1). In patients with larger, more severe cortical syndromes (TACS), an infarct was visible on both DWI and T2-WI in 8/13 (61%) patients, DWI being uniquely helpful in identifying recent infarction in only 31% (95%CI, 10-61%) of patients with a TACS. In patients with smaller anterior infarcts however (PACS or LACS), a recent infarct was demonstrated by DWI alone in greater proportions of patients (42% of PACS (95% CI 31-5%), and 43% of LACS (95% CI 28-59%). The proportion of patients in which DWI was rated as 'helpful' (identifying a relevant lesion not seen on T2-WI or distinguishing a new from an old lesion) also varied according to clinical subtype: DWI was 'helpful' in 31% of TACS, 62% of PACS, 62% of LACS, and 56% of POCS. DWI was of most use in patients with smaller cortical lesions (PACS and LACS, odds ratio 3.66, 95% CI 1.06 – 12.6) (figure 2). When DWI scans was reclassified as 'helpful' if they showed no new ischaemic lesion as well as distinguishing a new from an old infarct or demonstrating a recent ischaemic lesion, this observation was even more pronounced (88% of LACS compared to 39% TACS, odds ratio 11.8, $p = 0.003$, (figure 3). When clinical stroke severity was rated according to the CNS, the group of patients in which DWI was deemed to be 'helpful' (showing a recent lesion, distinguishing a new from an old infarct, or showing no new ischaemic lesion) had higher CNS scores (i.e. milder strokes), than the group in which DWI was 'unhelpful' ($p = 0.001$) (figure 4).

Figure 1. Utility study. The proportion of scans demonstrating recent infarction.

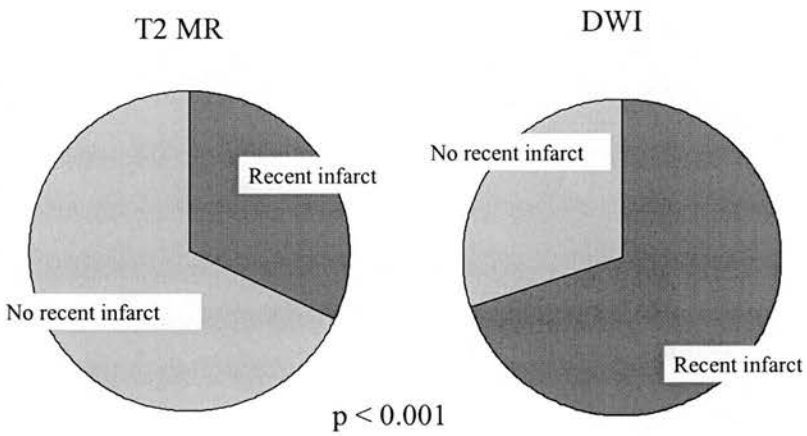


Figure 2. Utility study. DWI influence – DWI helpful if distinguishes recent infarct or new from old.

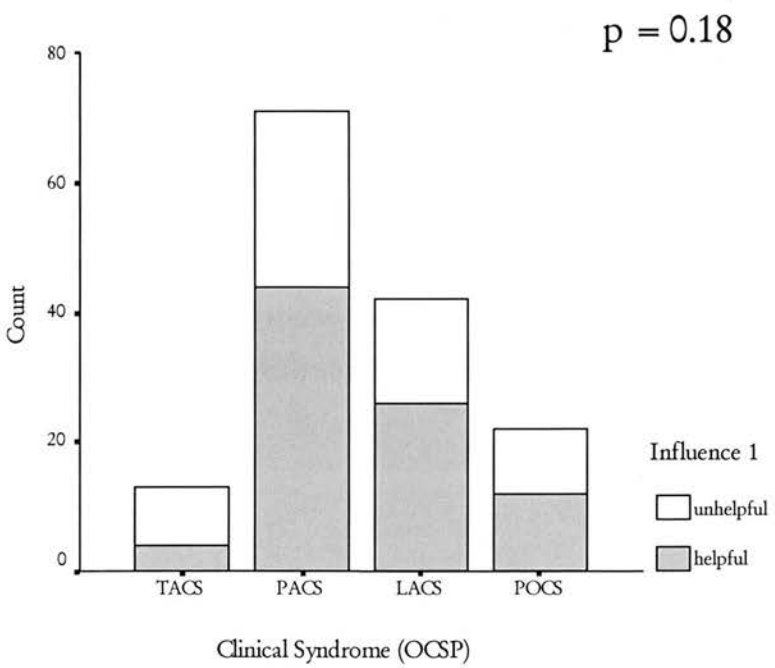


Figure 3. Utility study. DWI influence – DWI helpful if distinguishes recent infarct or new from old or is normal

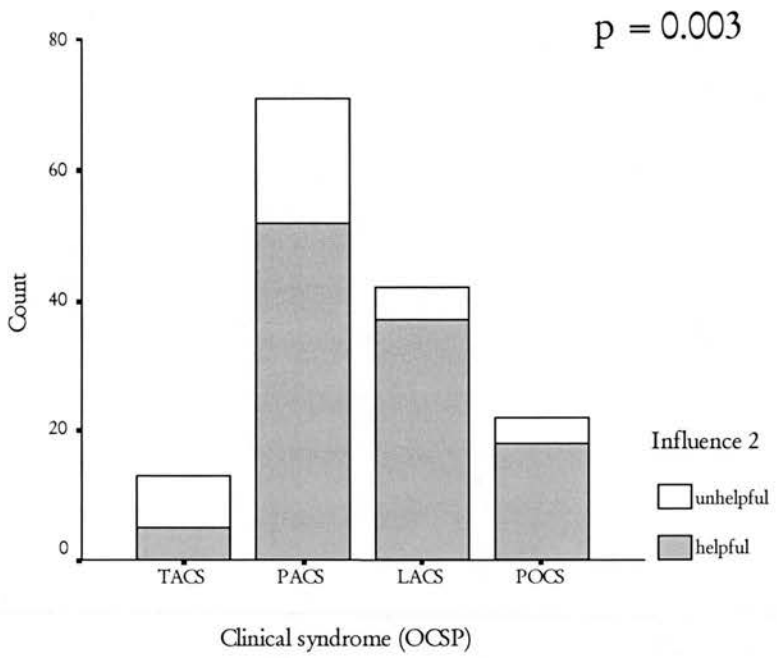
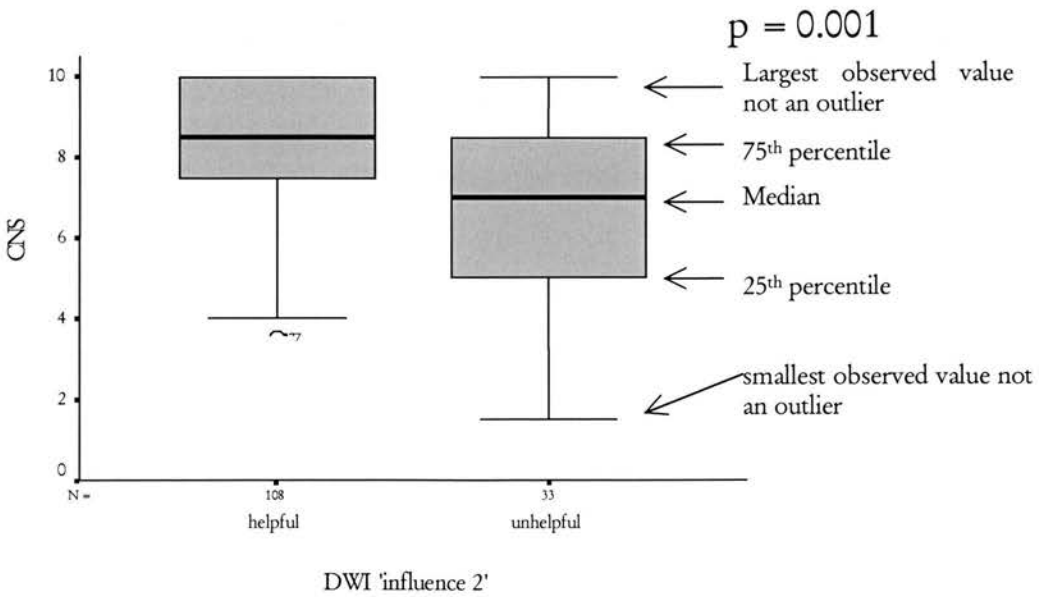


Figure 4. Canadian Neurological Score (CNS) and DWI influence (helpful if shows recent infarct, distinguishes new from old, or is normal



8.3.2 DWI and stroke severity

Patient baseline characteristics

108 subjects were scanned, 102 of whom presented with stroke, and five with TIA. In one patient, the diagnosis was undetermined. The median time from stroke to scanning was two days, mean time three days (standard deviation 4.2). Sixty-eight (63%) patients were scanned within two days, and 84 (78%) were scanned within three days (72 hours) of stroke onset, i.e. 15% were scanned on day three, and only 7% later than that.

In patients presenting with a stroke, 12 (11% of total scanned) had total anterior circulation syndromes (TACS); 52 (48%) had partial anterior circulation syndromes (PACS), 24 (22%) had lacunar syndromes (LACS); 14 (13%) had posterior circulation syndromes (POCS) (table 1). The CNS scores ranged from 1.5 (severe) to 10 (mild), median 8.0. There was no significant difference in the time lapse from stroke to MR imaging between either the OCSP subtypes ($p = 0.23$) or patients ranked according to their score on the Canadian Neurological Scale ($p = 0.42$).

Univariate analyses

Clinical features at baseline

There was a significant association between the clinical status of the patient as measured by the OCSP classification and the ADCr ($p = 0.002$). The mean ADCr values for patients with a TACS differed significantly from those with a LACS or POCS ($p = 0.006$, figure 5). The mean ADCr was also significantly lower in those with lower initial scores on CNS (correlation coefficient 0.30, $p = 0.01$, figure 6). There was a significant correlation between the initial severity as measured by the CNS and the visibility of lesion on T2-WI ($p = 0.007$, figure 7). The mean CNS score of patients with no lesion visible on T2 or DWI was significantly milder than those with both barely and easily visible lesions on T2-WI ($p = 0.023$ and 0.011 respectively). There was also an association between the clinical stroke severity measured by the CNS and the volume of

the visible lesion on DWI (correlation coefficient -0.23, p = 0.05) and between the OCSP classification and the lesion volume on DWI (p < 0.001).

Imaging features

ADCr was associated with the size of lesion seen on DWI, i.e. the larger the DWI lesion, the lower the ADCr (correlation coefficient -0.46, p = 0.05, figure 8). Note that some patients had very small lesions on DWI making measurement of the ADC value difficult. Patients with no visible lesion on DWI or where the lesion was simply too small to be able to measure ADCr without risk of including normal brain (n = 27) were not included in this particular analysis[26]. The ADCr was also associated with the visibility of lesion on T2-WI (p < 0.001, figure 9), i.e. the more visible the lesion on T2-WI, the lower the ADCr value.

Functional outcome

There was a significant association between the ADCr and outcome of the patients at six months (p = 0.009, figure 10). Patients who were dead or dependent at six months (Rankin value three to six) had lower baseline ADCr values than those who were alive and independent (Rankin zero to two) at six months. Patients who were dead or dependent at six months were also more likely to have visible lesions on T2-WI (chi squared, p = 0.18, odds ratio 1.8 (95% CI, 0.8-3.9)), and a large lesion on DWI (p = 0.17), although these associations were not significant.

Multivariate analyses

A simple forward, stepwise multiple logistic regression analysis was performed, using only three variables (age, stroke severity (CNS) and ADCr) because the size of the study population and the number of outcome events did not justify the inclusion of more than these key variables. Both increasing age and lower CNS score were more likely to be associated with a poor outcome (odds ratios 1.04 per year, 95% CI 0.76 to 1.43, p=0.01 and 1.82 per point on score, 95% CI 1.39 to 2.38, p<0.001 respectively). However,

using a forward stepwise analysis, the addition of ADCr to the model did not confer any additional benefit over and above age and stroke severity ($p = 0.26$). Thus, although reduced ADCr correlates with severe strokes, a more visible lesion on T2-WI and a larger lesion on DWI, it is not an independent predictor of functional outcome.

Figure 5. Severity study. Relationship between ADCr and initial clinical stroke syndrome (OCSP).

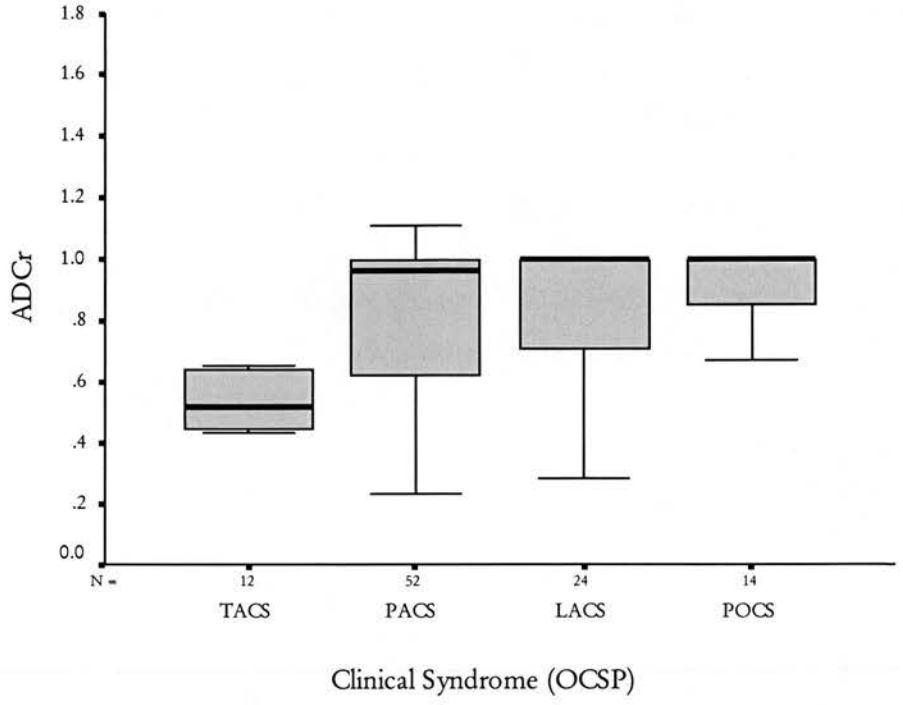


Figure 6. Severity study. Relationship between ADCr and stroke severity as defined by CNS (10 = mild stroke and 1.5 = severe stroke).

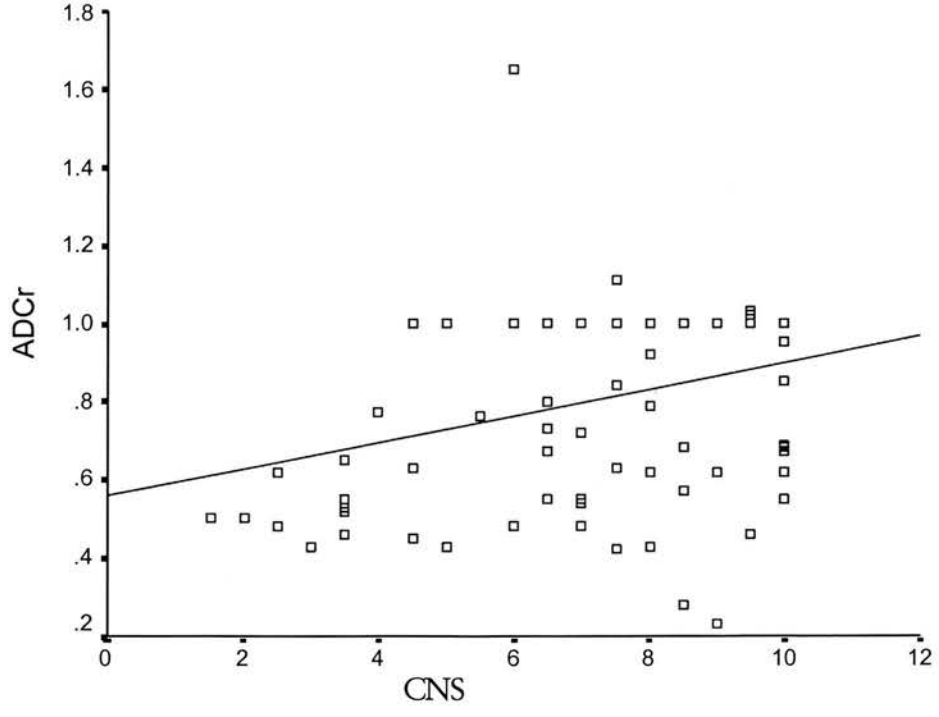


Figure 7. Severity study Relationship between initial stroke severity (CNS) and visibility of lesion onDWI and T2-WI.

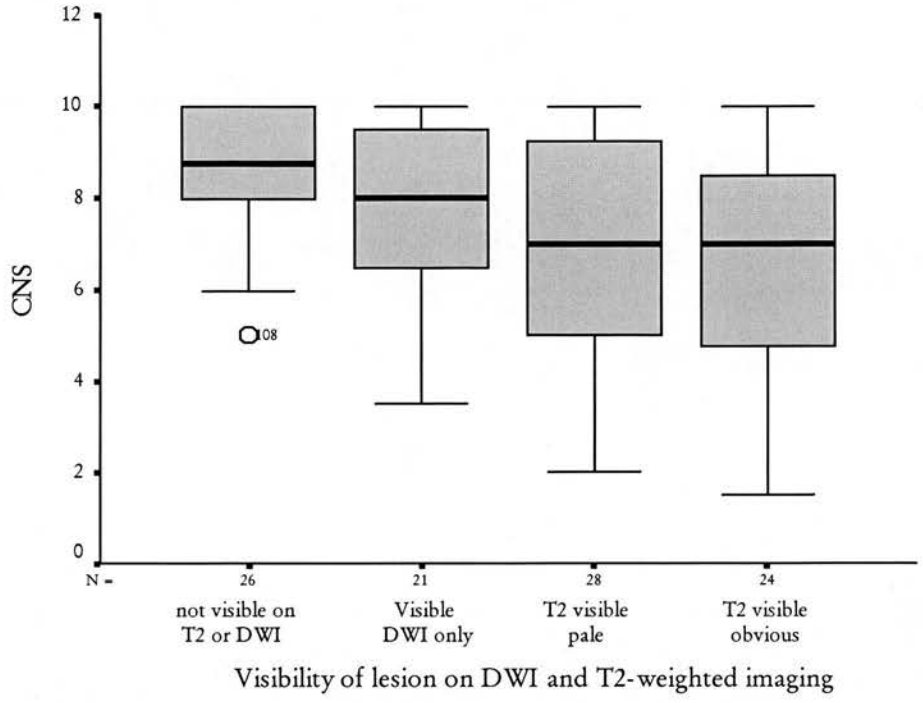


Figure 8. Severity study. Relationship between ADCr and the volume of lesion on DWI

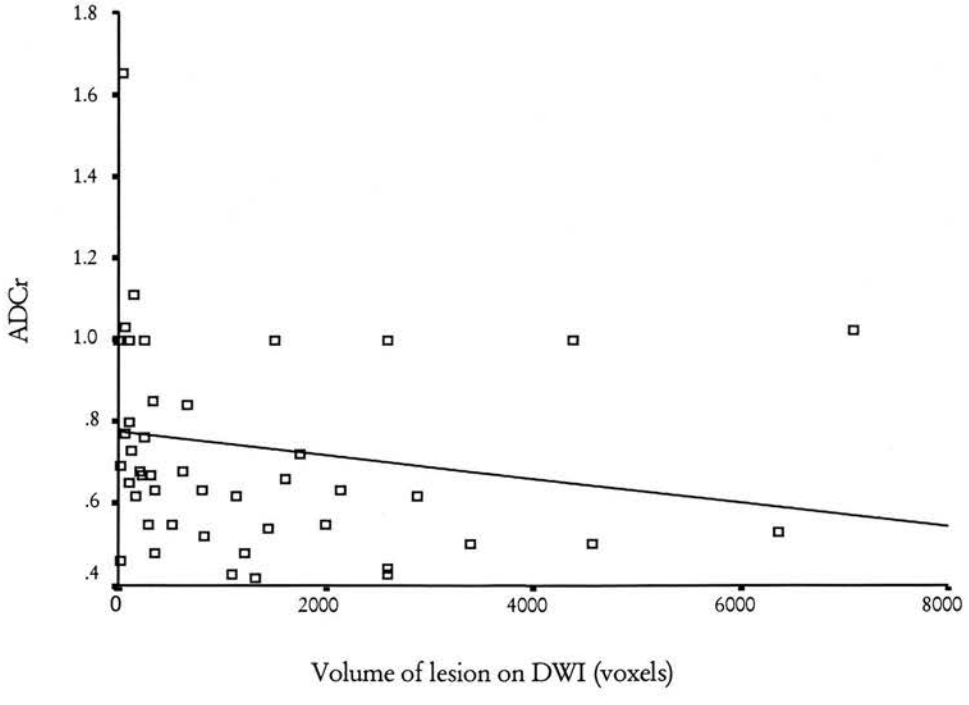


Figure 9. Severity study. Relationship between ADCr and visibility of lesion on T2-WI and DWI

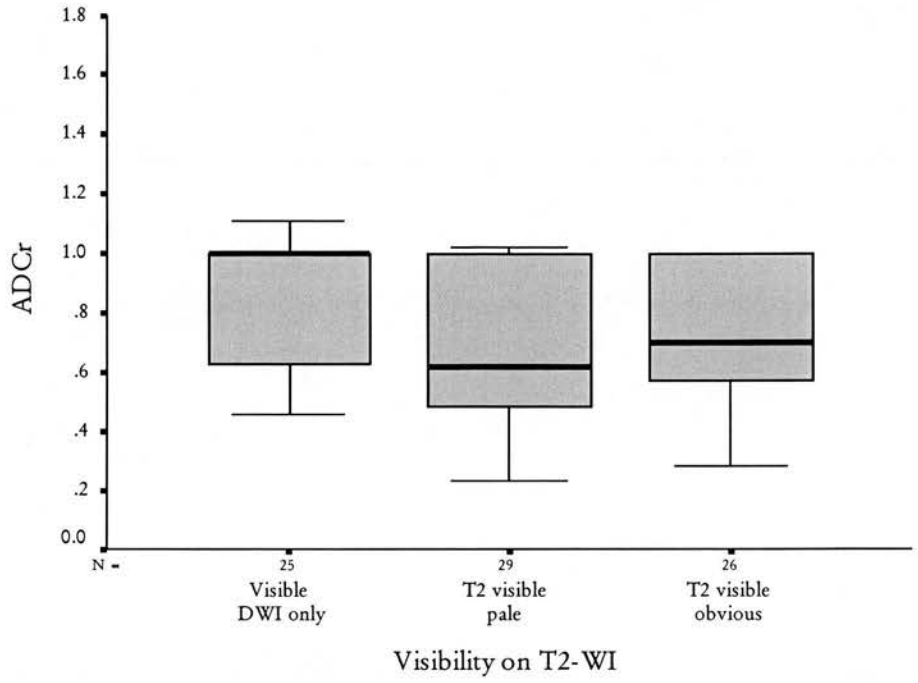
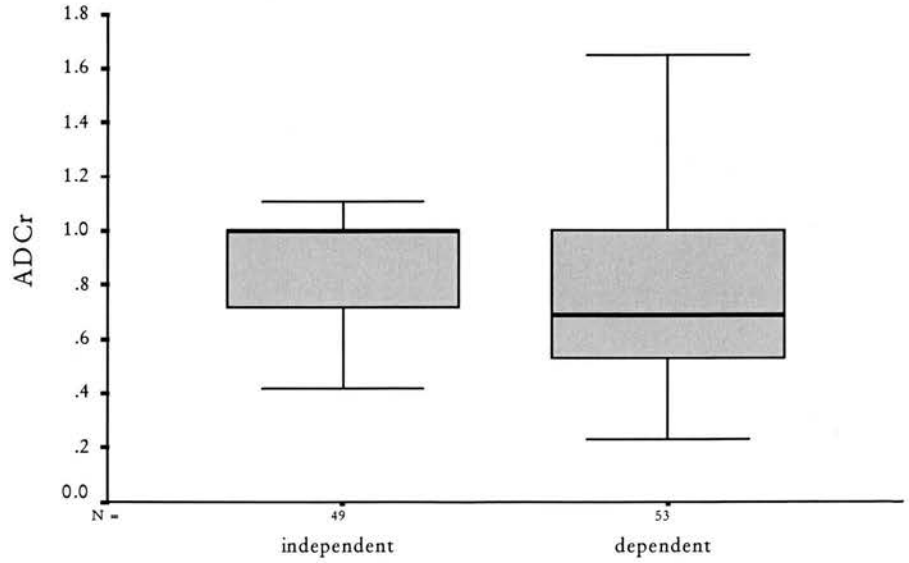


Figure 10. Severity study. Relationship between the ADCr and clinical outcome at six months according to the Rankin scale, where Rankin 0, 1, or 2 is independent and 3-5 is dependent and 6 is dead.



8.4 Discussion

The utility of DWI in stroke

Before a new imaging technique is accepted as the new investigative standard, it should have been shown to demonstrate new information relevant to the clinical management of the patient that cannot be demonstrated with existing technology. This information should be gained at no extra risk to the patient, or the information gained should be worth the extra risk[27]. DWI is undeniably an exciting development in the investigation of patients with stroke, but its true role needs to be defined. Stroke is an immense world-wide problem, and as yet, there are very few centres where access to MRI scanning is freely available on a 24-hour basis to all patients presenting with a stroke. If the main use of DWI is to confirm a hyperacute stroke, its usefulness will be limited to the very small fraction of patients presenting within a time frame that may make them eligible for consideration of hyperacute treatment[28]. However, this study suggests that DWI is actually of greater use in confirming the presence of an ischaemic lesion in patients with milder strokes and for days after the stroke even in outpatients, and not just in the hyperacute phase.

In this study we found that the patient groups in which DWI gave most information not available on conventional imaging were those with medium or small cortical lesions or lacunar lesions. As they are less severely affected, these patients often present outside the time window for hyperacute treatment, even as outpatients, where the clinical issue is ensuring appropriate secondary prevention. In patients with large strokes, the infarct was often visible on more conventional imaging, therefore DWI was felt to be less helpful in this group.

How does our study of clinical usefulness compare to previous studies?

Our study, which is the largest of its kind, agrees with earlier studies that found DWI more sensitive than conventional MRI, particularly in patients with mild stroke. Albers et al (40 patients) found that DWI identified clinically significant findings not seen on conventional MRI in 48% of patients and distinguished new from old lesions in 20% of

patients[29] (compared with 56% and 13% respectively in our study). Lansberg et al (52 patients) found that adding DWI to conventional MRI improved the accuracy of identifying acute stroke lesions (acute lesions were identified on conventional T2 MRI in 71% compared to 94% of DWI scans)[30]. Oliviera-Filho et al (67 patients) found that conventional MR imaging failed to demonstrate relevant lesions in around one quarter of consecutive patients with small-penetrator infarct, all of which had had relevant lesions demonstrated by DWI[31]. Rovira et al (100 patients) found that DWI added relevant clinical information in 42% of their case series of subcortical infarcts[32] over and above conventional MRI. Both our study and these previous studies provide data that help to delineate in whom, and for how long after stroke, DWI is superior to conventional imaging. This information is essential if there is a choice of imaging available. For example, in a patient having a large total anterior circulation stroke, there may be little information gained from DWI over and above that seen on CT[33]. Consequently, the potential risk to such a patient of using imaging that takes longer to acquire than CT (during which the patient has to lie on their back, at risk of aspiration, less accessible to medical staff) may not be justified. However, in the investigation of a patient with a stroke that could have more than one cause, such as infarcts in multiple territories due to cardioembolism, or a single territory due to carotid stenosis, the use of DWI to help distinguish between them[34-36], could accurately identify the most appropriate secondary prevention strategy.

If imaging is limited, to what groups of patients could DWI be targeted?

In the hyperacute setting when time is extremely limited, lesions on DWI may be easier for the less well trained observer to see, and may help guide clinical management. Also, in patients where there remains clinical uncertainty; up to 20 percent of patients presenting to hospital with stroke-like symptoms may not be having a stroke[37], and within the first day the conventional MRI or CT scans of a high proportion of patients with (milder) strokes may be normal[38]. In such cases, if repeat neuroimaging is not available, the only feature helping to distinguish stroke from non-strokes may be time, as other clinical signs become evident or other investigations reveal other diagnoses. In a small proportion of patients, this could present a delay in diagnosis that may be deemed unacceptable. In such cases, consideration should therefore be given to using

DWI, outside the hyperacute time-frame when it is important to determine a) whether the patient has truly had a new infarct, and b) exactly what part of the brain has been affected.

DWI and stroke severity

Ours is the largest study to date seeking to define the relationship between MR imaging parameters such as lesions on DWI, clinical stroke severity and functional outcome. We have identified that ADCr is indeed closely associated with the initial severity of the stroke, other imaging parameters and six month functional outcome in a univariate analysis, but not in a multivariate analysis taking account of age and stroke severity. Thus ADCr on its own is unlikely to be a useful surrogate outcome predictor because it is no better than the CNS (or equivalent clinical scale), which is quicker to obtain, much less expensive and less risky to the patient. A much larger dataset would be required to determine whether the ADCr is a weak independent prognostic variable. The close inter-relationships between different imaging features of the ischaemic lesion (size on DWI or visibility on T2-WI and ADCr) means that some imaging parameters may independently predict poor outcome but much more data would be needed to test this reliably. The close relationship between ADC and stroke severity means that careful clinical characterisation of patients and inclusion of clinical characteristics in the analysis is essential in studies where the purpose is to improve understanding of the interaction between imaging features like ADCr, and functional outcome. The present study clearly demonstrates that to be able to interpret changes in ADCr with any accuracy, stroke severity must be taken into account.

What are the limitations of the severity study?

Some patients were scanned relatively late after onset of their symptoms yet still included in this study. Contrary to initial reports[39], studies have demonstrated that ADCr values do not recover rapidly after stroke[20,40,41], and furthermore lesions may still be visible on DWI (regardless of ADC changes) up to three weeks after onset of symptoms[42]. Certainly some of the patients scanned in the present study at a relatively later time still had an abnormal ADCr. These patients reflect the fact that some patients

present late, usually after a minor stroke, and we need to know what to expect if they undergo DWI. However they were few in number.

We used two different MR imaging machines and two different techniques for obtaining diffusion images. However, we countered any effect that this might have had by using the ratio of the ADC in the infarct to that in normal brain.

What are the implications for other studies of the relationship between imaging parameters and stroke severity or outcome?

Patients with more severe strokes tend to be admitted to hospital sooner than milder strokes[43]. Therefore, it is possible that patients with more severe strokes, and so lower ADCr values, may also reach the scanner sooner after stroke than those with milder strokes and so higher ADCr values. There was no significant difference in the present study in the time of scanning severe strokes versus the milder strokes. However, previous studies that examined ADCr changes over time using 'snapshot' imaging of individual patients (rather than serial imaging of the same patients at different times), and observed low ADC values within the first few hours, and normal or high ADC values by 24 hours[39], may simply have been imaging severe strokes soon after stroke and milder strokes later (the artefact of case-mix). Studies in which the same subjects were scanned sequentially avoid the case-mix problem and show that the infarct ADC may actually remain low for two weeks or more after stroke [19,23] [18,20,41,41].

Previous smaller studies have shown a relationship between lesion volume on DWI and functional outcome (total number of patients 145)[14,16,18,44], as well as other imaging parameters and outcome (35 patients)[17,45] in univariate analyses. Warach et al (81 patients) also found associations between DWI lesion volume and hypoperfused lesion volume in 81 patients randomised in the citacholine trial[46]. We have not found a statistically significant association between DWI lesion volume and outcome, possibly because our patient group reflected a broader case mix than was included in previous studies. However we did find other imaging parameters that were associated with clinical outcome, albeit not independently after clinical stroke severity and age had been taken into consideration. This does not mean that there is no association between

imaging features and clinical outcome, but merely that they are so closely associated with clinical stroke severity that huge sample sizes are needed to identify small independent associations.

What next for DWI?

The next challenge for DWI is to improve understanding of exactly what the lesions seen (and their associated ADC values) mean. In animal studies, DWI lesions can recover completely[47], and studies in humans have found patients with a definite recent stroke but no visible lesion on DWI[48]. Therefore, a lesion on DWI cannot as yet be taken to distinguish unsalvageable from salvageable tissue reliably. At the moment, the ADC value that represents a 'cut-off', i.e. that distinguishes definitely unrecoverable from recoverable tissue, is not precisely known. The use of an arbitrary cut off (e.g. a 40% reduction in ADCr[19,20], may risk missing a substantial amount of permanently damaged tissue in patients with milder strokes (note figure 5). The 40% reduction was identified from a study of mostly severe strokes[20]. In the present study, the ADCr values of most patients with a PACS or LACS were reduced by less than 40% (ie only about 20% reduced), so the lesion would have been missed on an automated analysis set to identify 40% or more reduction. A 40% reduction would however in the present study have distinguished virtually all TACS from PACS, LACS and POCS (figure 5) so might be useful for that purpose, i.e. early identification of a subset of bad strokes. Although we did not do late follow-up imaging, the functional outcome scores of the patients with PACS and LACS (about 50% were dependent or dead) would suggest that most of the DWI-visible lesion in these patients was actually permanently damaged tissue, despite the fact that the mean ADCr in the patients with a PACS or a LACS was reduced by less than 40% (figure 1). In other words, these patients would not have met the 40% ADCr reduction for 'permanent damage' that has been suggested. Automated ADCr measurement methods will require careful calibration so as not to overlook significantly damaged tissue if too low an ADCr level is used[49]. Our results suggest that the ADCr 'cut-off' value indicating permanent damage may well be different for different severities of stroke. Thus the "threshold" value would need to be adjusted accordingly. Furthermore, simultaneous integration of information from DWI, T2 and perhaps perfusion imaging[49] may be needed to achieve adequate tissue damage level

discrimination, rather than just relying on one imaging parameter. However, much more information will be required to achieve this degree of sophistication.

Conclusion

DWI does demonstrate more ischaemic lesions than conventional imaging and as such may prove valuable in the management of patients in terms of both acute treatment and secondary prevention. The ADCr may be a powerful way of quantifying the degree of ischaemic damage, and as such is an exciting step forward in the management of stroke. However, much more careful quantification of the relationship of the ADC to time, stroke severity and the possibility of recovery are needed before we can interpret a specific ADC value precisely, and therefore use ADC as a surrogate outcome measure or determine the contribution of diffusion-weighted imaging to future stroke care.

Table 1. Baseline characteristics of patients in DWI utility study

	Mean	Median	Range	Standard deviation
Age (years)	67.6	69	19 - 93	15.6
Time (days)	6.1	2	< 1 - 77	10.1
CNS:	8	8.5	1.5 - 10	2

Table 2. Baseline characteristics of patients in DWI and stroke severity study

	Mean	Median	Range	Standard deviation
Age (years)	67.8	70	19 - 93	16.8
Time (days)	3	2	< 1 - 31	4.2
CNS:	7.5	8.0	1.5 - 10	2.5

Table 3. Clinical severity of stroke patients according to OCSP classification in DWI and stroke severity study

Syndrome	Number (data complete)	Median age, years (range)	Median CNS (range)	Median time from onset of symptoms to scan, days (range, SD)	Percentage dead or dependent at six months
TACS	12 (10)	73 (53 – 93)	4.0 (1.5 – 7)	1 (0-31, 8.6)	100
PACS	52 (48)	73 (38 – 93)	7.5 (2.5 – 10)	2 (0-23, 5.1)	50
LACS	24 (24)	67 (27 – 89)	8.5 (2.5 – 10)	2 (0-14, 2.7)	46
POCS	14 (12)	61 (19 – 87)	10 (6.5 – 10)	1 (0-5, 1.8)	29
TIA	5 (4)	60 (31 – 76)	9.8 (8 – 10)	2 (0-2, 0.9)	50

1. Barber PA, Darby DG, Desmond PM, Gerraty RP, Yang Q, Li T et al. Identification of major ischemic change: Diffusion-weighted imaging versus computed tomography. Stroke 1999;30:2059-65.

2. Lansberg MG, Albers GW, Beaulieu C, Marks MP. Comparison of diffusion-weighted MRI and CT in acute stroke. Neurology 2000;54:1557-61.

3. Albers GW, Lansberg MG, Norbash AM, Tong DC, O'Brien MW, Woolfenden AR et al. Yield of diffusion-weighted MRI for detection of potentially relevant findings in stroke patients. Neurology 2000;54:1562-7.

4. Gonzalez RG, Schaefer PW, Buonanno FS, Schwamm LH, Budzik RF, Rordorf G et al. Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset. Radiology 1999;210:155-62.

5. Moulin T, Cattin F, Crepin-Leblond T, Tatu L, Chavot D, Piotin M et al. Early CT signs in acute middle cerebral artery infarction: predictive value for subsequent infarct locations and outcome. Neurology 1996;47:366-75.

6. von Kummer R, Nolte PN, Schnittger H, Thron A, Ringelstein EB. Detectability of cerebral hemisphere ischaemic infarcts by CT within 6 h of stroke. Neuroradiology 1996;38:31-3.

7. Uchino K,.Cramer S. Criteria and baseline characteristics predict outcome in acute stroke trials. Stroke 2000;31:277.

8. von Kummer R,.Gahn G. Comparison of diffusion-weighted MRI and CT in acute stroke. Neurology 2000;55:1760.

9. Hakan A, Oliviera-Filho J, Buonanno FS, Ezzeddine M, Schaefer PW, Rordorf G et al. Diffusion-weighted imaging identifies a subset of lacunar infarction associated with embolic source. Stroke 1999;30:2644-50.

10. Kumon Y, Zenke K, Kusunoki K, Oka Y, Sadamoto K, Ohue S et al. Diagnostic use of isotropic diffusion-weighted MRI in patients with ischaemic stroke: detection of the lesion responsible for the clinical deficit. Neuroradiology 1999;41:777-84.

11. Wardlaw JM, Lewis SC, Dennis MS, Counsell C, McDowall M. Is visible infarction on computed tomography associated with an adverse prognosis in acute ischemic stroke? Stroke 1998;29:1315-9.

12. Toni D, Iweins F, von Kummer R, Busse O, Bogousslavsky J, Falcou A et al. Identification of lacunar infarcts before thrombolysis in the ECASS I study. Neurology 2000;54:684-8.

13. Provenzale JM,.Sorensen AG. Diffusion-weighted MR imaging in acute stroke: theoretic considerations and clinical applications. AJR 1999;173:1459-67.

14. Tong DC, Yenari MA, Albers GW, O'Brien M, Marks MP, Moseley ME. Correlation of perfusion- and diffusion weighted MRI with NIHss score in acute (<6.5 hour) ischaemic stroke. Neurology 1998;50:864-70.

15. Warach S, Dashe JF, Edelman RR. Clinical outcome in ischaemic stroke predicted by early diffusion-weighted and perfusion magnetic resonance imaging: a preliminary analysis. Journal of Cerebral Blood Flow & Metabolism 1996;16:53-9.

16. Lovblad KO, Baird AE, Schlaug G, Benfield A, Siewert B, Voetsch B et al. Ischemic lesion volumes in acute stroke by diffusion-weighted magnetic resonance imaging correlate with clinical outcome. Ann Neurol 1997;42:164-70.

17. Beaulieu C, de Crespigny A, Tong DC, Moseley ME, Albers GW, Marks MP. Longitudinal magnetic resonance imaging study of perfusion and diffusion in stroke: Evolution of lesion volume and correlation with clinical outcome. Ann Neurol 1999;46:568-78.

18. Barber PA, Darby DG, Desmond PM, Yang Q, Gerraty RP, Jolley D. Prediction of stroke outcome with echoplanar perfusion- and diffusion-weighted MRI. Neurology 1998;51 :418-26.

19. Schlaug G, Benfield A, Baird AE, Siewert B, Lovblad KO, Parker RA et al. The ischemic penumbra: operationally defined by diffusion and perfusion MRI. Neurology 1999;53:1528-37.

20. Schlaug G, Siewert B, Benfield A, Edelman RR, Warach S. Time course of the apparent diffusion coefficient (ADC) abnormality in human stroke. Neurology 1997;49:113-9.

21. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-7.

22. de Crespigny AJ, Marks MP, Enzmann DR, Moseley ME. Navigated diffusion imaging of normal and ischemic human brain. Magnetic Resonance in Medicine 1995;33:720-8.

23. Mattielo J, Basser P, Le Bihan D. The b matrix in diffusion tensor echo-planar imaging. Magn Reson.Med. 1997;37:292-300.

24. Ulug A, Beauchamp N, Bryan RN, van Zijl PCM. Absolute quantitation of diffusion constants in human stroke. Stroke 1997;28:483-90.

25. Counsell, C. The prediction of outcome in patients with acute stroke. Thesis , 21-22. 1997. University of Cambridge.

26. Laubach HJ, Jakob PM, Lovblad KO, et al. A phantom for diffusion-weighted imaging of acute stroke. JMRI 1998;8:2136-40.

27. Jarvik JG, Haynor DR, Longstreth WT, Jr. Assessing the usefulness of diagnostic tests. Am J Neuroradiol 1996;17:1255-8.

28. Chiu D, Krieger D, Villar-Cordova C, Kasner SE, Morgenstern LB, Bratina et al. Intravenous tissue plasminogen activator for acute ischemic stroke: feasibility, safety, and efficacy in the first year of clinical practice. Stroke 1998;29:18-22.

29. Albers GW, Lansberg MG, Norbash AM, Tong DC, O'Brien MW, Woolfenden AR et al. Yield of diffusion-weighted MRI for detection of potentially relevant findings in stroke patients. Neurology 2000;54:1562-7.

30. Lansberg MG, Norbash AM, Marks MP, Tong DC, Moseley ME, Albers GW. Advantages of adding diffusion-weighted magnetic resonance imaging to conventional magnetic resonance imaging for evaluating acute stroke. Arch.Neurol. 2000;57:1311-6.

31. Oliveira-Filho J, Ay H, Schaefer PW, Buonanno FS, Chang Y, Gonzalez et al. Diffusion-weighted magnetic resonance imaging identifies the "clinically relevant" small-penetrator infarcts. Archives of Neurology 2000;57:1009-14.

32. Rovira A, Pedraza S, Molina C, Capellades J, Grive E, Rovira A et al. Diffusion-weighted magnetic resonance in the diagnosis of acute subcortical infarcts. Revista de Neurologia 2000;30:914-9.

33. Barber PA, Demchuk AM, Hill M, Pexman W, Hudon M, Tomanek A et al. A comparison of CT versus MR imaging in acute stroke using ASPECTS: will the 'new' replace the 'old' as the preferred imaging modality? Stroke 2001;31:325.

34. Ay H, Oliveira-Filho J, Buonanno FS, Ezzeddine M, Schaefer PW, Rordorf G et al. Diffusion-weighted imaging identifies a subset of lacunar infarction associated with embolic source. Stroke 1999;30:2644-50.

35. Roh JK, Kang DW, Lee SH, Yoon BW, Chang KH. Significance of acute multiple brain infarction on diffusion-weighted imaging. Stroke 2000;31:688-94.

36. Baird AE, Lovblad KO, Schlaug G, Edelman RR, Warach S. Multiple acute stroke syndrome: Marker of embolic disease? Neurology 2000;54:674-8.

37. Libman RB, Wirkowski E, Alvir J, Rao TH. Conditions that mimic stroke in the emergency department. Implications for acute stroke trials. Archives of Neurology 1995;52:1119-22.

38. Toni D, Iweins F, von Kummer R, Busse O, Bogousslavsky J, Falcou A et al. Identification of lacunar infarcts before thrombolysis in the ECASS I study. Neurology 2000;54:684-8.

39. Welch KMA, Windham RA, Knight RA, Nagesh V, Hugg JW, Jacobs M. A model to predict the histopathology of human stroke using diffusion and T2-weighted magnetic resonance imaging. Stroke 1995;26:1983-9.

40. Bastin ME, Rana AK, Wardlaw JM, Armitage PA, Keir SL. A study of apparent diffusion coefficient of grey and white matter in human ischaemic stroke. Neuroreport 2000;11:2867-74.

41. Yang Q, Tress BM, Barber PA, Desmond PM, Darby DG, Gerraty RP et al. Serial study of apparent diffusion coefficient and anisotropy in patients with acute stroke. Stroke 1999;30:2382-90.

42. Wardlaw JM, Armitage P, Dennis MS, Lewis S, Marshall I, Sellar R. The use of diffusion-weighted magnetic resonance imaging to identify infarctions in patients with minor strokes. J Stroke Cerebrovasc Dis 2000;70-5.

43. Uchino K,.Cramer S. Criteria and baseline characteristics predict outcome in acute stroke trials. Stroke 2000;31:277.

44. van Everdingen KJ, van, der Grond J, Kappelle LJ, Ramos LM, Mali WP. Diffusion-weighted magnetic resonance imaging in acute stroke. Stroke 1998;29:1783-90.

45. Schwamm LH, Koroshetz WJ, Sorensen G, Wang B, Copen WA. Time course of lesion developoment in patients with acute stroke. Serial diffusion- and hemodynamic-weighted magnetic resonance imaging. Stroke 1998;29:2268-76.

46. Warach S, Pettigrew LC, Dashe JF, Pullicino P, Lefkowitz DM, Sabounjian L et al. Effect of citicoline on ischemic lesions as measured by diffusion- weighted magnetic resonance imaging. Citicoline 010 Investigators [In Process Citation]. Ann.Neurol. 2000;48:713-22.

47. Minematsu K, Li L, Sotak CH, Davis MA, Fisher M. Reversible focal ischemic injury demonstrated by diffusion-weighted magnetic resonance imaging. Stroke 1992;23:1304-10.

48. Ay H, Buonanno FS, Rordorf G, Schaefer PW, Schwamm LH, Wu O et al. Normal diffusion-weighted MRI during stroke-like deficits. Neurology 1999;52:1784-92.

49. Jacobs MA, Knight RA, Soltanian-Zadeh H, Zheng ZG, Goussev AV, Peck DJ et al. Unsupervised segmentation of multiparameter MRI in experimental cerebral ischemia with comparison to T2, diffusion, and ADC MRI parameters and histopathological validation. J.Magn Reson.Imaging 2000;11:425-37.

Summary

Neuroimaging has a number of important roles in the management of patients with stroke. It is used:

- To exclude non-stroke pathology;
- To distinguish ischaemia from haemorrhage;
- To determine the extent of damage (for example, identifying intraventricular extension in intracerebral haemorrhage, the volume of involved territory in ischaemia);
- To detect complications such as hydrocephalus, oedema, haemorrhagic transformation;
- To investigate the state of intracerebral vessels, identifying occlusion or rupture;
- To determine the site of a lesion, thereby helping to deduce its cause, or assess suitability for surgery; and
- As an aid in clinical outcome prediction; and in the future, as the ischaemic penumbra is better characterised, as a surrogate clinical marker.

The use of CT in stroke has increased markedly within the last ten years, as has MRI, although MRI is still used far less frequently than CT. The beneficial effect of aspirin following ischaemic stroke has made it important to distinguish ischaemic stroke from intracerebral haemorrhage (ICH). The advent of thrombolysis, as well as ongoing research into other acute therapies, is making it increasingly important to define more accurately the site and extent of ischaemic damage.

Thus, as the availability and choice of neuroimaging has increased, so has the complexity of information the stroke physician requires from it. Information on the relative strengths and weaknesses of CT, conventional MRI and DWI are needed to make best use of a resource that has many competing demands made upon it from other specialities. Even if geography or financial constraints restrict the choice of scanner (or timing of access to it), it is important to be aware of what it can and can not do.

Not scanning patients with stroke, or not scanning with CT rapidly enough, may miss ICH. Not identifying ICH has important consequences both for the accuracy of epidemiological data (and consequently any dependent research, such as genetics studies), and for patient care. The risk of anticoagulants in acute ICH may be self-evident but the limited data available for antithrombotic drugs in this setting also include the possibility of harm.

The ideal imaging modality to identify haemorrhage varies depending upon the timing of scanning. The limited information available from the literature as well as new data from our CT versus MRI study show that signs of haemorrhage can be easily identified on CT very soon after onset of stroke symptoms but these can disappear without trace within a matter of days. Both the CT versus MRI study, and the late haemorrhage study confirm that MRI is superior to CT in the demonstration of haemorrhage at a later time point, and that with the correct MRI sequence, signs can be identified for many years after the event. The CT versus MRI study demonstrated that neuroimaging has important effects on patient care. Scanning with CT increased clinical certainty of diagnosis and use of MRI increased certainty that an ICH is not being missed. Results of MRI led to changes to secondary prevention strategies for patients with previously unidentified ICH.

In the CT versus MRI study, CT and conventional MRI were equally good at demonstrating ischaemic lesions, but both failed to demonstrate a lesion in around 50% of patients. Our study of the clinical usefulness of DWI showed that DWI was far better than conventional MRI at detecting ischaemic lesions, and delivered clinically relevant information not gained from conventional imaging in a high proportion of patients. Our study of the relationship between clinical stroke severity, apparent diffusion coefficient (ADC) value and visibility of lesions on DWI demonstrated the relationship between the clinical status of the patient and the ADC and hence lesion visibility.

Performing systematic reviews of imaging literature revealed disturbing weaknesses of methodology in the majority of published studies. This weakness is not just historical; methods used in recent DWI and PI studies are barely any better than those of studies published on CT one or even two decades ago. Small samples of highly selected patients,

undergoing imaging that is often interpreted without blinding has resulted in weak, subjective data that is impossible to generalise. On the evidence of these reviews, performing a systematic review of imaging literature with the aim of extracting data with which to compare imaging modalities has little point. However, they do perform an important role in highlighting the consistent study weaknesses that, if addressed, will improve the data that is collected.

Neuroimaging is vital for stroke management, but if performed inappropriately, will deliver less information, or less accurate information than it has the potential to. Appropriate attention must be paid to the sensitivity and specificity of imaging techniques in order to make best use of them. Without sufficient attention, any dependent research, for instance into potential treatments using surrogate markers, will be at best delayed, and at worst, wholly inaccurate.

Acknowledgements

My research was funded by the National Coordinating Centre for Health Technology Assessment, a branch of the National Health Service Research and Development body. The statements, opinions and results in this thesis are mine and do not reflect the policy or position of the NCCHTA.

I would like to thank the IST and CAST collaborative groups for allowing access to their data. I would also like to thank: my supervisor Professor Joanna Wardlaw for reading so many scans, as well as for her advice and unflagging support; Professor Martin Dennis for completing numerous decision forms as well as his sage comments on the thesis, Professor Charles Warlow for his lecture in Bristol that inspired me to learn more about stroke and apply for the Fellowship that got the ball rolling; Professor Peter Sandercock, Dr Richard Lindley, Dr Gillian Mead, Dr Peter Hand, Dr Jo Kwan, Dr Rustam Al Shahi, Dr Eivind Berge for all completing decision forms in such a strikingly uncomplaining fashion; Dr Steff Lewis for her easy to understand statistical advice; Ann Deary, David Perry, Mike McDowall, Sheila Grant, Hazel Fraser and Brenda Thomas for their time and support; and my fellow research fellows for their sizeable contribution, along with the previously mentioned people, in making my time in the Department of Neurosciences such an enjoyable experience.

Last but obviously not least, I would like to thank my partner Rachel, and my family: Margery, Belinda and Mark, Andrew and Val; for everything.

My Contribution To This Thesis

I performed the systematic reviews that formed the basis of chapters 2, 3, 4, 6 and 7, personally entering data into Microsoft Access Databases. In chapter 3, as well as performing the analysis upon the IST and CAST haemorrhagic strokes dataset, I hand-searched all individual patient record forms.

For the CT versus MRI study, I designed the Access databases in which data was stored, and created the data entry forms used by the neuroradiologist reporting the scans, and the doctors answering clinical questions. I identified patient case notes in order that histories and ancillary investigations could be recorded, prepared anonymised histories, and recruited a proportion of the patients. I also entered the data into Access, and Excel and SPSS in order to analyse the data.

For the DWI studies, I recruited the majority of the patients, assessing them prior to imaging. I compiled a database of patients and analysed the data.

Work from chapters 2 and 5 has been the basis of platform presentations at the 2000 and 2001 European Stroke Conferences. Work from chapter 3 was presented in poster form at the 2000 American Stroke Conference and has been accepted for publication in Cerebrovascular Diseases. Work from chapter 8 has been presented as poster and platform presentations the 2001 British Association of Stroke Physicians and accepted for publication in Neurology. The systematic review featured in chapter 7 was published in Stroke, November 2000.

This thesis was composed by myself, the research undertaken in Edinburgh, and has not been submitted for candidature for any other degree, postgraduate diploma or professional qualification.

Appendices and Publications

Appendix I. Classification systems for ischaemic stroke

a) Bamford Classification

Groups patients into four categories that define the site and size of the stroke, and gives an indication of their likely outcome. Patients will present with the following combination of symptoms:

i) Total Anterior Circulation Infarct (TACI) – disorder of higher cerebral dysfunction (e.g. dysphasia), homonymous visual field defect, and ipsilateral motor/sensory deficit.

ii) Partial Anterior Circulation Infarct (PACI) – two of the three components of the TACI, or with a motor or sensory deficit more restricted than would be classified as LACI

iii) Lacunar Infarct (LACI) - pure motor stroke, pure sensory stroke, sensori-motor stroke, or ataxic hemiparesis

iv) Posterior circulation Infarct (POCI) – ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit, bilateral motor and/or sensory deficit, disorder of conjugate eye movement, cerebellar dysfunction without ipsilateral long-tract deficit, isolated homonymous visual field deficit.

b) TOAST classification

Separates patients into five categories based on the presumed aetiology of the ischaemic stroke, and makes use of brain imaging, cardiac imaging, and Doppler ultrasound of extracranial arteries.

i) Large-artery atherosclerosis (embolus/thrombosis)*
ii) Cardioembolism (high-risk/medium risk)*
iii) Small-vessel occlusion (lacune)*
iv) Stroke of other determined aetiology*
v) Stroke of undetermined aetiology
    a. Two or more causes identified
    b. Negative evaluation
    c. Incomplete evaluation

*Possible or probable depending on results of ancillary studies

Appendix II. Clinical scoring systems for distinguishing intracerebral haemorrhage and ischaemic stroke

1. Siraraj Stroke Score (SSS)

SSS = (2.5 x consciousness) + (2 x vomiting)
+ (2 x headache)
+ (0.1 x diastolic blood pressure)
- (3 x atheroma) – 12

Clinical ratings

Clinical Status	Score
Consciousness	
Alert	0
Drowsy/Stupor	1
Semicoma/Coma	2
Vomiting headache within 2 hours	
No	0
Yes	1
Atheroma (diabetic history, angina, claudication)	
None	0
One or more	1

Diagnosis

> 1	Cerebral haemorrhage
< -1	Cerebral infarction
-1 to 1	Uncertain diagnosis

2. Allen Score

Multiply blood pressure by 0.17 and add to total of clinical rating scores below

Clinical ratings

Clinical feature	Standardised coefficient	Clinical status	Score
Apoplectic onset Loss of consciousness Headache within 2 h Vomiting Neck stiffness	+0.63112	One or none of these Two or more	0 +21.9
Level of consciousness (24 h after admission)	+0.45950	Alert Drowsy Unconscious	0 +7.3 +14.6
Plantar responses	+0.29369	Both flexor/single extensor Both extensor	0 +7.1
Diastolic BP (24 h after admission)	+0.26843	BP in mm mercury	+(BP x 0.17)
Atheroma markers (angina, claudication, diabetes)	-0.17685	None One or more	0 -3.7
History of hypertension	-0.20039	Not present Present	0 -4.1
Previous event (TIA or stroke)	-0.31229	None Any number of events	0 -6.7
Heart disease	0.45065	None Aortic or mitral murmur Cardiac failure Cardiomyopathy Atrial fibrillation Cardiomegaly MI within 6 months	0 -4.3 -4.3 -4.3 -4.3 -4.3 -4.3
		Constant	-12.6

Diagnosis

<+4 probability of infarction is >90%

>+24 probability of haemorrhage is >90%

Appendix III. Electronic search strategies

Glossary of search terms

/	MEDLINE subject heading (MESH)
mp.	Title, abstract, heading word, trade name, manufacturer name
.tw	Identifies the word specified in the title or abstract
ti.	Identifies word specified in title
$	Identifies any word beginning with the text preceding it
or	In the search parameter specified, the article only has to be found in one of the search terms
and	In the search specified, the article must be found in all search terms

Expanded search strategy for stroke.

Table1. EMBASE

	Search History
1	exp cerebrovasc disease/
2	stroke$.tw
3	cerebrovascular$.tw
4	(cerebral or cerebellar or brainstem or vertebrobasilar).tw
5	(infarct$ or isch?emi$ or thrombo$ or emboli$).tw
6	4 and 5
7	carotid$.tw
8	(cerebral or intraventricular or brainstem or cerebellar).tw
9	(infratentorial or supratentorial or subarachnoid).tw
10	(brain or intraventricular or brainstem or cerebellar).tw
11	8 or 9 or 10
12	(haemorrhage or hemorrhage or haematoma or hematoma).tw
13	(bleeding or aneurysm).tw
14	12 or 13
15	11 and 14
16	thrombo$.tw
17	(intracranial or (venous adj5 sinus$) or (sagittal adj5 venous) or sagittal vein).tw
18	16 and 17
19	transient isch?emic attack$.tw
20	reversible isch?emic neurologic$ deficit$.tw
21	venous malformation$.tw
22	arteriovenous malformation$.tw
23	21 or 22
24	11 and 23
25	exp aphasia/
26	dysphasia/
27	hemianopia/
28	hemiplegia/
29	hemiparesis/
30	(aphasi$ or dysphasi$ or hemianop$).tw
31	(hemipleg$ or hemipar$).tw
32	exp carotid artery surgery/
33	Or/1-3, 6-7, 18-20, 24-32

Table 2. MEDLINE

	Search History
1	exp cerebrovascular disorders/
2	stroke$.tw
3	cerebrovascular$.tw
4	(cerebral or cerebellar or brainstem or vertebrobasilar).tw
5	(infarct$ or isch?emi$ or thrombo$ or emboli$).tw
6	4 and 5
7	carotid$.tw
8	(cerebral or intracerebral or intracranial or parenchymal).tw
9	(brain or intraventricular or brainstem or cerebellar).tw
10	(infratentorial or supratentorial or subarachnoid).tw
11	8 or 9 or 10
12	(haemorrhage or hemorrhage or haematoma or hematoma).tw
13	(bleeding or aneurysm).tw
14	12 or 13
15	11 and 14
16	thrombo$.tw
17	(intracranial or (venous adj5 sinus$) or sagittal adj5 venous) or (sagittal adj5 vein)).tw
18	16 and 17
19	transient isch?emic attack$.tw
20	reversible isch?emic neurologic$ deficit.tw
21	venous malformation$.tw
22	arteriovenous malformation$.tw
23	21 or 22
24	11 and 23
25	exp aphasia/
26	hemianopsia/
27	hemiplegia/
28	(aphasi$ or dysphasi$ or hemianop$).tw
29	(hemiplegi$ or hemipar$).tw
30	25 or 26 or 27 or 28 or 29
31	or/1-3, 6-7, 15, 18-20, 24, 30
32	leukomalacia, periventricular/
33	cerebral anoxia/
34	exp dementia, vascular/
35	exp vascular headache/
36	migrain$.tw
37	32 or 33 or 34 or 35 or 36
38	31 not 37

Appendix IV. Glossary of MR imaging parameters

TR	Relaxation time (ms)
TE	Excitation time (ms)
NEX	Number of excitations
PD	Proton density
FLAIR	Fluid attenuated inversion recovery
GRE	Gradient echo

Appendix V. Canadian Stroke Scale

Clinical status	Score
Mentation	
Level of consciousness	
Alert	3
Drowsy	1.5
Orientation	
Oriented	1
Disorientated/ not applicable	0
Speech	
Normal	1
Expressive deficit	0.5
Receptive deficit	0
Motor function – no comprehension deficit	
Face	
None	0.5
Present	0
Arm: proximal	
None	1.5
Mild	1
Significant	0.5
Total	0
Arm: distal	
None	1.5
Mild	1
Significant	0.5
Total	0
Leg	
None	1.5
Mild	1
Significant	0.5
Total	0
Motor response – comprehension deficit	
Face	
Symmetrical	0.5
Asymmetrical	0
Arms	
Equal	1.5
Unequal	0
Legs	
Equal	1.5
Unequal	0

Appendix VI. CT versus MRI study: patient acceptability questionnaire

Patient preference sheet

Thank you for helping us in our research by having both the CT scan and the MR scan.

Please answer these few questions before leaving the department.
Please give this form to the radiographer before you leave.
(Please circle your answer to each question below).

Which test did you have first?	CT	MR
Which test did you prefer?	CT	MR
Would you have a CT scan again if you had to?		Y/N
If no, please say why:		
Would you have an MR scan again if you had to?		Y/N
If no, please say why:		

Any other comments?

Thank you for your help.

Appendix VII. CT versus MRI study. Form for recording CT and MRI results.

(*LSR – Lothian Stroke Register, DCN – department of neurosciences)

CT Scan report

LSR* Number

DCN* XR Number

Event to Scan time

Xray History

Scan finding

Recent infarct ☐

Recent infarct with haemorrhagic transformation ☐

Recent haemorrhage ☐

Old lesion probable infarct ☐

Old lesion probable haemorrhage ☐

Multiple periventricular lucencies ☐

Cerebral atrophy ☐

Normal scan ☐

Other comments

Appendix VIII. CT versus MRI study. Form for recording doctors decisions.

Doctor's dilemmas – interpretation with CT scan

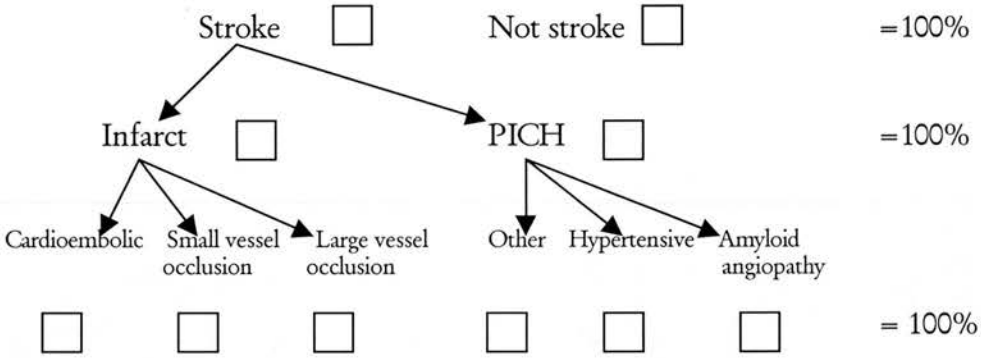
Doctor deciding ☐ Doppler:

LSR Number ☐

Bamford classification ☐ Echo:

ECG:

a) Type of event, and how sure are you? (0-100%)



b) Management decisions

i) Aspirin

Start aspirin ☐

Stop aspirin ☐

Continue aspirin ☐

Start another antiplatelet agent ☐

Not relevant ☐

ii) Anticoagulation

Start anticoagulant ☐

Stop anticoagulant ☐

Continue anticoagulant ☐

Not relevant ☐

iii) Endarterectomy

Refer for endarterectomy ☐

Not relevant ☐

iv) Other – specify

Appendix IX. The Rankin outcome scale

Clinical status	Score
No symptoms	0
Minor symptoms which do not interfere with lifestyle	1
Some restriction to lifestyle, but look after themselves	2
Significant restriction to lifestyle, preventing total independence	3
Severe handicap preventing independent existence but not requiring constant attention	4
Severe handicap, totally dependent, requiring attention day and night	5
Dead	6

Systematic Review of Diffusion and Perfusion Imaging in Acute Ischemic Stroke

S.L. Keir, MRCP; J.M. Wardlaw, FRCR

Background and Purpose—Recent advances in neuroimaging have raised hopes of early and accurate identification of ischemic brain and the discrimination of dead from salvageable tissue. We sought to determine whether the data published so far are enough to establish the roles of these techniques in everyday clinical practice.

Methods—A systematic review of studies of MR diffusion-weighted imaging (DWI), perfusion imaging (PI), or a combination of the two, in human stroke, excluding abstracts and case reports. One reviewer extracted information on the size of each study, its main purpose, methodological details, and results.

Results—We identified 47 studies of DWI, 18 studies of MR PI alone or in combination with another advanced imaging modality, and 19 studies of DWI and PI together. Although high proportions of the studies were prospective and gave good details of the imaging sequences used, the majority gave very limited details on patient selection and clinical characteristics or blinded imaging assessment. Pathophysiological changes were inferred from DWI/PI patterns that were not supported by other data.

Conclusions—Despite considerable enthusiasm for and promise of these techniques, there is not sufficient information available in these studies to enable us to draw firm conclusions about the sensitivity and specificity of these techniques for identification of either ischemic lesions not visible by other means or salvageable tissue. Future studies should include larger numbers of carefully described patients, assess the contribution of DWI over and above other imaging, obtain follow-up at an appropriate time interval to determine accurate clinical and neuroradiological outcomes, and assess DWI/PI abnormality with reperfusion in randomized treatment trials. Investigators should also be encouraged to combine their individual patient data in meta-analyses to obtain a more robust assessment of the value of DWI and PI from larger sample sizes. **(*Stroke*. 2000;31:2723-2731.)**

Key Words: magnetic resonance imaging, diffusion-weighted ■ magnetic resonance imaging, perfusion-weighted ■ stroke, acute ■ stroke, ischemic

Recent advances in brain imaging may likely underpin the future of stroke care. In particular, the introduction of MR and development of advanced imaging-like spectroscopy (MRS) and diffusion-weighted and perfusion imaging (DWI and PI, respectively) have raised hopes of greater ability to discriminate dead from salvageable tissue and thus to target new treatments. Several reviews[1,2] have summarized the technical aspects and possible applications of these advances, and considerable enthusiasm has been expressed for the use of these techniques in stroke; relatively few, however, have highlighted the problems that need to be overcome to maximize the potential of these exciting techniques.[3,4]

DWI works on the principle that sensitizing a standard MR image to diffusion weighting identifies regions of abnormal water movement, occurring very early after onset of ischemia, resulting in increased (bright) signal intensity.[5] It is thought that visualization of lesions at such an early stage might identify patients before acute stroke treatment. The degree of water movement abnormality (or tissue injury) may be quantified by calculating the apparent diffusion coefficient (ADC).[2]

PI can detect hypoperfused regions of brain either by monitoring the transit of a rapidly injected contrast agent[6] or magnetically tagged water molecules in arterial blood[7] through the brain. In regions distal to an arterial occlusion, the arrival of the contrast agent or tagged water molecules may be delayed. The resulting signal-time curve can be converted into a concentration-time curve, from which several functions that describe regional perfusion can be determined.

Combining DWI and PI may enable visualization of the abnormal area soon after the onset of symptoms (previously, one would expect CT or T2-weighted MR to show an infarct) and provide information that may discriminate dead from still-recoverable brain. In hyperacute stroke treatment, this could help identify which patients are most likely to benefit from potentially risky treatments.

A study to investigate a new imaging procedure should give clear details of its aim, the definition and characteriza-

Received April 4, 2000; final revision received June 26, 2000; accepted June 30, 2000.

From the Department of Clinical Neurosciences, Western General Hospital NHS Trust, Edinburgh, UK.

Correspondence to Dr S. Keir, Department of Clinical Neurosciences, Western General Hospital NHS Trust, Bramwell Dott Building, Crewe Road, Edinburgh EH4 2XU, UK. E-mail slk@skull.dcn.ed.ac.uk

***Stroke* is available at http://www.strokeaha.org**

tion of its study population (eg, severity and type of ischemic stroke), the technical details of the imaging tests, whether the analysis was prospective or retrospective, how the images were analyzed and read, and whether the reading was blinded to clinical details and other imaging. If comparisons within the study population are made, an objective statistical analysis should be used to compare the populations with a null hypothesis being clearly stated. Thus, before we can establish the role of these advanced imaging techniques, we need to be confident that studies have demonstrated the efficacy, feasibility, and the reliability of the information so derived and that they do indeed identify patients for specific reasons not possible by other means. We therefore undertook a systematic review of all published studies of DWI, PI, or both in patients with stroke to see how well the above criteria had been met, what information had been obtained so far on patient characterization and acute stroke treatment guidance, and where more information on DWI and PI might be needed, and so where future research with DWI and PI should be directed.

Methods

We used the Cochrane Database of Systematic Reviews methodology[8] to perform this systematic review. This methodology has been developed for undertaking systematic reviews of randomized controlled treatment trials, but the same principles apply to the conduct of systematic reviews of diagnostic tests and observational studies. We have used these methods successfully previously to study risks for and diagnosis of unruptured intracranial aneurysms.[9]

Search Strategy

We searched for all published articles on DWI, PI, or a combination of the two in the English and non-English language literature in MEDLINE and EMBASE from October 31, 1999, back to the earliest studies available (using the search terms "diffusion weighted," "perfusion weighted," "dynamic susceptibility," "hemodynamically weighted," expanded to maximize the number of hits, and combined these with the Cochrane library search strategy for stroke,[8] hand-searched 6 relevant journals *(Stroke, Radiology, American Journal of Neuroradiology, American Journal of Roentgenology, Magnetic Resonance in Medicine, Journal of Magnetic Resonance Imaging*) from November 1999 to January 2000, and examined reference lists in the identified articles.

Inclusion criteria: published studies in which DWI, PI, or both in combination had been conducted in humans with stroke. We excluded case reports and studies that had so far only appeared in abstract form. Where there was any doubt about the inclusion or exclusion of a study, the paper was discussed and a consensus opinion was reached.

Data Extraction and Analysis

One reviewer (S.K.) extracted information on the sample size of each study, its main purpose (ie, use of imaging to predict outcome, technical development of the imaging technique, comparison with another imaging technique), the time window from onset of stroke symptoms to imaging, how the diagnosis of stroke had been made and by whom (ie, stroke physician, neurologist, general physician, or not stated), the patient inclusion criteria, whether the patients had received any stroke treatment and whether this was randomized, the DWI or PI scanning method, the image analysis method, whether interpretation of diffusion or perfusion images was blinded to clinical details and the results of other imaging modalities, whether any patients had been imaged but then excluded from further analysis and why, whether any data on clinical outcome had been collected and at what time after stroke, and the overall conclusion of the study.

Analysis

The extracted information was entered into an ACCESS database and assessed with descriptive statistics.

Results

Forty-seven studies concerned specifically with DWI in humans with ischemic stroke were identified (total number of patients=2436, median 34). Also identified were 14 studies concerning MR PI alone (n=198, median 10); 4 combining MR PI with another advanced imaging modality, such as single-photon emission computed tomography (SPECT; n=38, median 10); and 19 studies concerning the combination of DWI and MR PI (n=563, median 21).

General Methodological Details of All Studies

Sample populations ranged from 3 to 224 patients. In these studies, although the technical information on the imaging sequences was good, the information on general methodological details (blinding, patient selection and exclusions, and the proportion of uninterpretable scans) was limited, and generally these details were not mentioned. For instance, in the DWI-only studies, only 9 of 47 (<20%) mentioned that scans were interpreted by researchers blinded to clinical details or other imaging,[10–18] and only 6 (13%) gave specific details on patient inclusions and exclusions.[10,16,17,19–21] Only 9 studies gave details on the number (and reasons for) inadequate scans that were excluded from further analysis,[16,17,19,21–26] although it is likely that patients with poor-quality scans were excluded from the analysis in other studies. There were no details in any of the studies on patient tolerability of the investigation (Figures 1, 2, and 3).

Studies of DWI Alone

The 47 studies of DWI had the following primary purposes (some studies had >1 primary purpose): technical development of the imaging sequence or analysis method (17 studies); change in visibility of lesions on DWI or ADC over time (6 studies); correlation of DWI with measures of neurological severity (2 studies); comparison with CT or T2 MR to see whether DWI showed more lesions (11 studies); distinguishing old from new lesions (6 studies); use of DWI to demonstrate ischemic lesions in patients with TIA or lacunar stroke (4 studies); and feasibility of DWI in acutely ill patients (6 studies). Two studies addressed identification of hemorrhage on DWI and 1 addressed the important issue of negative DWI in patients with strokelike deficits.[27] These will be described in turn.

Seventeen (36%) studies (total n=567) investigated DWI techniques or refinements of techniques of image acquisition or processing, or methods of calculation of the apparent diffusion coefficient (ADC).[14,16,19,22–24,26,28–37] No useful comparisons could be made between them, as they all covered different technical aspects of the imaging and mentioned little about the type of patients included.

Six (13%) studies (including a total of 564 patients) studied the visibility of DWI lesions or changes in ADC values over time. One study repeatedly scanned the majority of the patients in the study[21] and found reduced ADC values up to 85 days after stroke. In the rest of the studies, the proportion

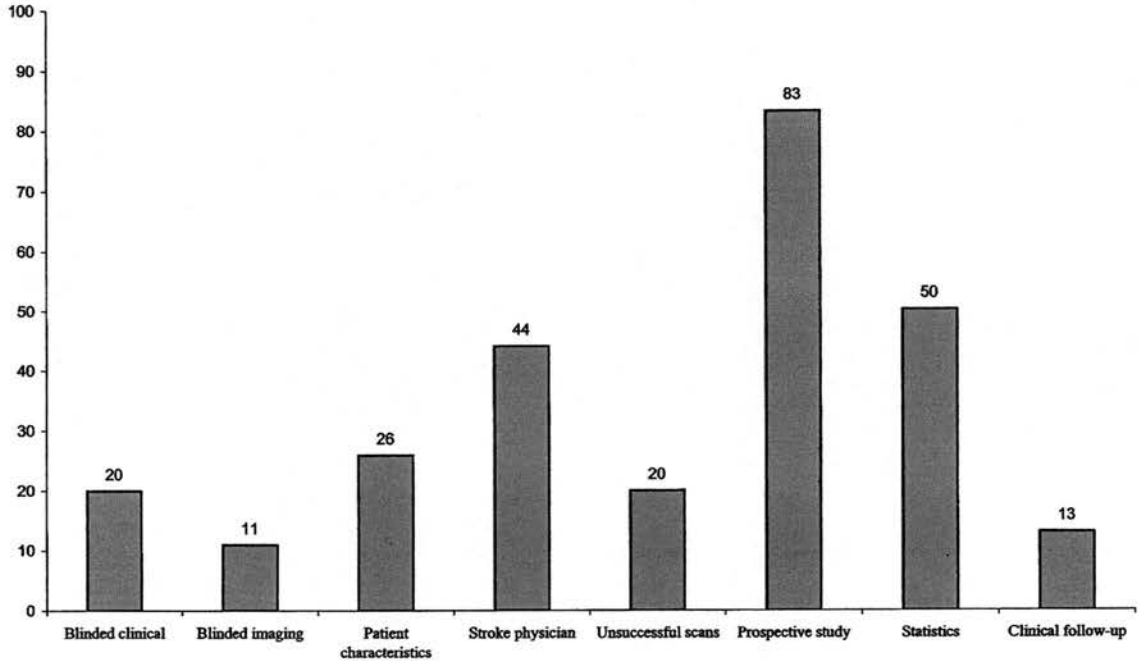


Figure 1. Proportion of studies documenting information, DWI (%).

of patients who had repeated scanning was much more limited[38–40] or impossible to determine.[15,41] In these studies, the time over which the DWI lesion remained visible was inferred by using scans of different patients at different time points, rather than repeated imaging of the same patient. Using only "snapshots" of different individual patients means that it is difficult to be precise about when a particular lesion may disappear, or an ADC value change.

Two (4%) studies (including 92 patients) investigated the correlation of early DWI (within 24[12] and 60[17] hours) with measures of clinical stroke severity at the time of imaging and at either 3[17] or 42 weeks.[12] Both studies demonstrated that acute lesion volumes on DWI correlated with the National Institutes of Health Stroke Scale (NIHSS) scores both acutely and at follow-up. In both studies, images were read blinded to clinical details, and in one[17] to initial T2 MR. However, as infarction visualized on all imaging modalities tested so far correlates with stroke severity, knowledge that DWI also correlates does not add significantly to the body of knowledge.

Eleven (23%) studies (total n=399) suggested that DWI demonstrated more lesions in the symptomatic anatomical area at an earlier time point than did conventional imaging. Although one study directly compared CT and DWI[10]

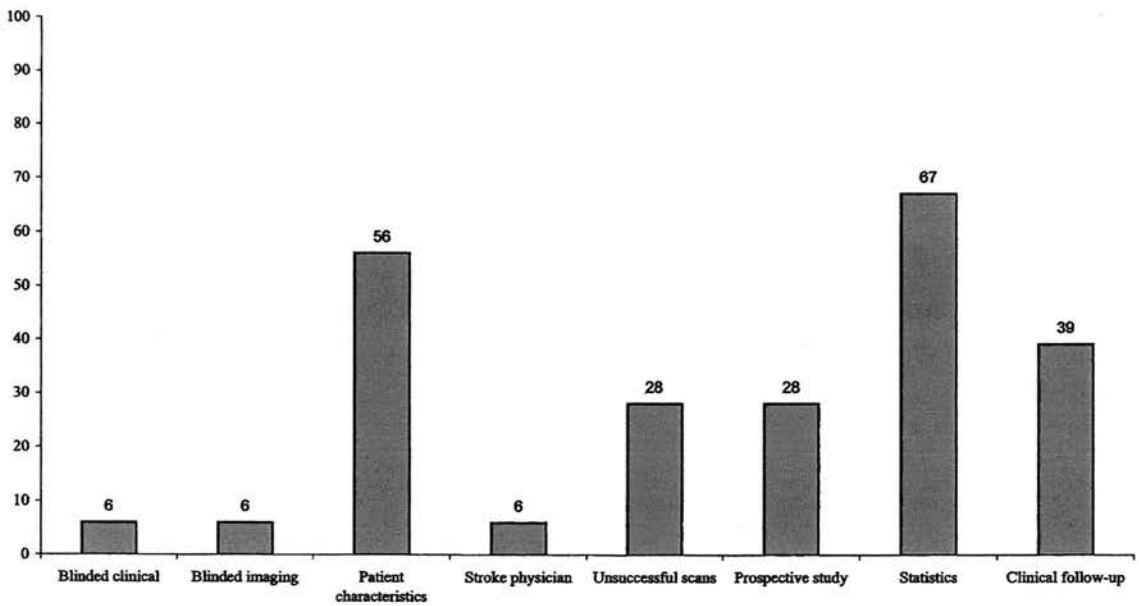


Figure 2. Proportion of studies documenting information, PI (%).

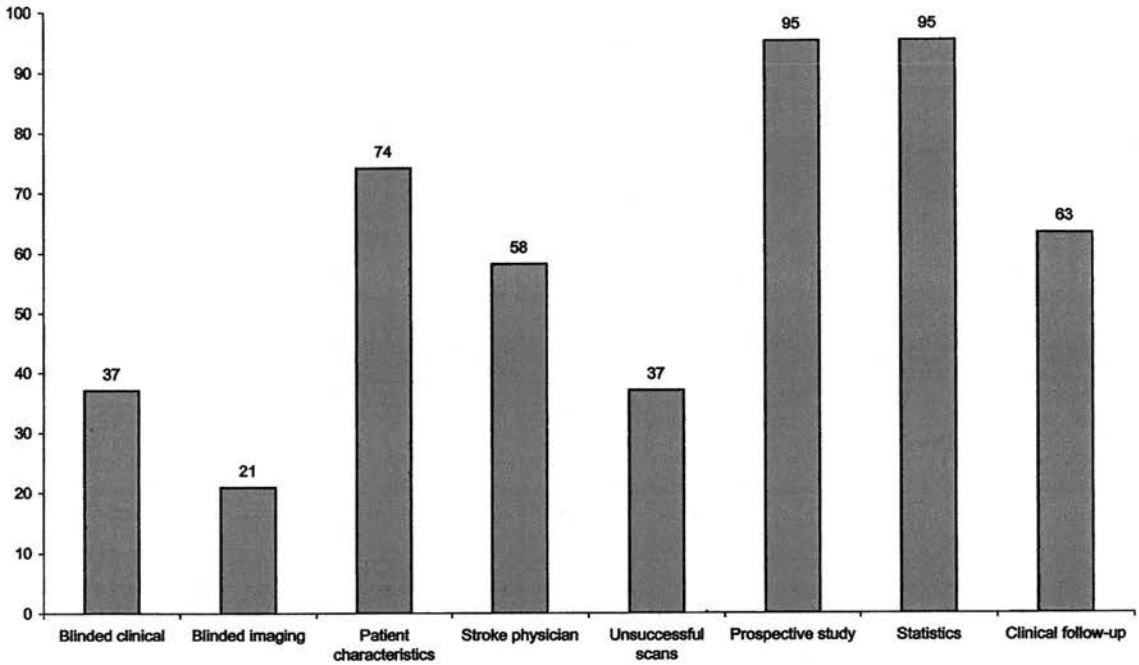


Figure 3. Proportion of studies documenting information, DWI/PI (%).

(n=17), the majority of studies compared DWI to conventional MR.[15,18,25,40,42–47] All of these studies indicated that more lesions were visible on DWI than on conventional imaging: in 5 studies, within 6 hours or less,[10,15,40,43,45] in 2 studies within 48 hours,[44,46] in 2 studies within 4 days,[18,42] and in 1 study "the time period under investigation" (8 hours to 12 days).[25] In only 2 of the studies the scans were read by observers blind to clinical details,[15,18] in only 1 study blind to other imaging,[43] and in only 1 the observers were blind to both clinical details and other imaging,[10] ie, in fewer than one third of studies purporting to show that DWI was better than conventional imaging was an attempt made to reduce bias by blinding the DWI interpretation. None mentioned whether an attempt was made to randomize the order in which the DWI and conventional imaging were performed or stated the order in which imaging was actually performed (ie, whether DWI was always performed after conventional imaging, in which case DWI would always be likely to show more lesions, or vice versa). The sample sizes in these studies ranged from 9 to 103 patients, which is too small to determine accurately the benefit of DWI. The proportion of patients in which DWI was felt to be superior to conventional MR ranged widely, from 5% to 71%. In 1 study it was impossible to define in how many patients DWI had proved to be superior.[47]

Six of 399 studies (13%) found that in patients with multiple lesions demonstrated on MR, it was possible to distinguish new from old lesions with DWI, with the acute lesion appearing hyperintense and the old hypointense on the DWI.[16,18,25,41,48,49] Timing of scanning from onset of symptoms ranged from less than seven hours to 11 days. In only 2 studies were the scans read blinded to clinical details.[16,18] The proportion of patients in which DWI was said to distinguish new from old lesions better than did conventional MR ranged from four to 15 out of about 220 patients with multiple lesions, ie, less than 10% of the total number of patients included.

Four (8%) studies (n=159) concentrated on the clinicotopography of a specific stroke subtype such as lacunar stroke[13,45,18] or transient ischemic attack.[50] The studies concentrating on lacunar symptoms demonstrated that DWI could identify appropriate subcortical areas of ischemia. The one study concerned with transient ischemic attacks demonstrated that 48% of patients whose symptoms resolved within 24 hours had relevant lesions on DWI within 24 hours of symptom onset. Patients whose symptoms resolved by 24 hours had smaller and less obvious lesions on DWI than patients whose symptoms had lasted longer.[50] Nonetheless, as with CT scanning,[51] this means that DWI cannot be used to discriminate between symptoms that will turn out to be TIAs and those that will turn out to be strokes.

Six (13%) studies (n=518), two of which were retrospective analyses, addressed the feasibility of undertaking an advanced imaging protocol in acutely ill stroke patients and suggested that it was possible.[20,26,32,42,46,50] None of the imaging was read blinded, which is clinically realistic, but data on patient inclusion and exclusions, as well as clinical characteristics was often limited, ie, information to identify patients who would be poor subjects for DWI was not given. Two studies (which included 20 patients with cerebral hemorrhage) demonstrated that it was possible to identify acute hemorrhage, a subset of patients previously thought to present difficulty on DWI,[52,53] although as neither study was blinded to other imaging results, the validity of this conclusion must be questioned.

One retrospective study (n =27) raised the important issue of patients with strokelike deficits and negative DWI imaging[27] and explained that specificity had not been addressed because their entire (and substantial) case series (782 pa-

tients) had not been reviewed. Such a task would indeed have been a major undertaking, but it would have given us information on sensitivity and specificity of DWI with an accuracy that smaller studies which have attempted to address this issue[18] have not achieved. Other studies have attempted to define specificity and sensitivity of DWI,[20,43] but selection bias make it difficult to extrapolate these values to the general population with strokelike symptoms.

Studies of PI Alone

One of the 14 studies of PI alone attempted to evaluate the clinical usefulness of PI[54] (n=15); the other 13 studies (n=183) concentrated on the technical aspects of demonstrating abnormalities of regional cerebral perfusion.[6,7,55–65] All but 1,[64] which attempted to quantify the arterial input function (a constant required for the calculation of absolute blood flow), assessed relative rather than absolute cerebral blood flow. All studies used the gadolinium bolus tracking method of measuring blood transit time. A variety of perfusion abnormalities were demonstrated; 1 study[56] (n=11) noted a heterogeneous distribution of rCBF in the expected regions of interest in all examinations; 3[6,7,55] (n=16 to n=34) documented hyperperfusion as well as delayed or absent perfusion in the region of interest; and 1[54] (n=11) documented no perfusion deficits in 4 of the 11 subjects despite marked clinical signs and repeat MR within 48 hours confirming infarction.

Of the 4 studies that combined MR PI with another advanced imaging modality, perfusion MRI was correlated with SPECT findings in 3[66–68] and with xenon CT in 1.[69] All found that MR perfusion techniques correlated well with the perfusion deficit demonstrated on these other modalities. Sample sizes were small, and it was not made clear whether perfusion images were read by researchers blinded to other forms of imaging.

DWI and PI in Combination

Nineteen studies were identified, with a total sample size of 563 (median 21). The main purpose of 3 of the studies was to document the clinicotopography of the combined imaging[70–72]; one of these[71] documented important data on the variety of patterns of DWI and PI seen. However, sample size was small, and it was not clear whether DWI and PI were read with blinding to clinical details. One study compared the combination to CT in relation to acute determination of intracerebral hemorrhage,[73] but no details were given about whether the DWI was read with blinding to the CT. One study set out to determine the clinical feasibility of a combined protocol[74]; the resulting data were very encouraging with respect to the speed of the process but were lacking in patient clinical characteristics and, importantly, the proportion of patients the imaged group represented in relation to the total number of patients with stroke symptoms presenting to the study hospital.

Fourteen studies (74%; total sample size 316) were mainly concerned with the use of DWI/PI in predicting either the final size of infarct on conventional imaging[75–80] or final infarct size and clinical outcome.[81–88] The median sample size was 20 patients, and 4 of these studies reported inclusion of patients from previously published papers. Follow-up imaging was performed between 3 and 277 (median 8) days after initial scanning. Note that if "final infarct size" is measured at approximately 7 days or less, the infarct will be edematous and the mass effect will lead to overestimation of infarct size[89]; at approximately 10 to 21 days, "fogging"[90] obscures the infarct and so will lead to an underestimation of infarct size; and at 2 to 6 months, atrophy and ex vacuo effect will lead to underestimation of infarct size. Thus, timing is crucial for assessment of final infarct size, and many studies used too early a time point. Those that used later time points did not make clear whether ex vacuo effects were taken into account.

Varying patterns of "mismatch" between lesion extent on DWI and PI were seen and opinions given as to what these patterns represented. When PI lesions were larger than DWI, investigators inferred that a larger area of brain was under threat of ischemia than that outlined by the DWI lesion, ie, an ischemic penumbra. When DWI lesions were larger than PI lesions, or no associated PI lesion was visible, the investigators inferred that a degree of reperfusion had occurred but that an area of permanent damage, represented by the DWI lesion, had already occurred. When no DWI lesion was visible in the presence of a PI deficit, the investigators inferred that there was an acute arterial occlusion but no ischemic damage at the time of imaging.[84] Eleven studies (n=225) used MR angiography in their imaging protocols as well as PI and DWI, some of which helped to support the findings of the PI by demonstrating an appropriately occluded artery[71–73,77,78,80,82–85,87]; otherwise, there was no objective way in any of the studies for substantiating the "mismatch" theory. It is difficult to judge how robust the mismatch theory is, because the proportion of patients in whom the lesion had behaved as predicted on the follow-up imaging (ie, where PI>DWI, the area of ischemia on the follow-up scan increased in size) varied from 100%[78] to only 56%.[87]

Three of the studies that compared DWI/PI with final infarct size commented on the nature of the lesion visualized by DWI. Opinions varied; 1 study[75] implied that the DWI lesion was infarcted tissue, another stated that "DWI lesions do not reflect closely the extent of functionally compromised tissue,"[84] and another[76] stated that diffusion abnormalities indicated reversible and irreversible ischemia. However, it was not clear on what evidence these statements were based.

In the 9 studies that related DWI/PI patterns to clinical outcome (n=219), clinical follow-up ranged from 1 to 90 days after stroke. The scales used varied, the most common being the NIHSS, which is a measure of neurological deficit and not functional outcome.[75,81,82,85,86,88] Lesion size on acute DWI or PI correlated with final clinical outcome using the NIHSS, the Canadian Neurological Scale (CNS),[83,84] and the European Stroke Scale (ESS).[87] Because previous studies have shown that lesion size on imaging (eg, CT) correlated well with stroke severity, neurological deficit, and clinical outcome, it is hardly surprising that DWI/PI also correlates. The key question is what does DWI/PI *add* over and above any information already known from previously available imaging?

Discussion

Stroke medicine is now in an era of acute intervention, and practical imaging techniques that help confirm an ischemic

insult within minutes of the event and determine the amount of salvageable brain tissue remaining would obviously be invaluable tools. Hence the great flurry of enthusiasm around the exciting results of DWI and PI studies. The studies imply that DWI identifies definitely (permanently) damaged tissue and that DWI/PI mismatch identifies tissue at risk but still salvageable. Is this correct? Acute stroke imaging has come a long way in the last decade, but what has it really told us and where do we go from here?

We had hoped to determine the sensitivity and specificity of DWI for identifying acute ischemic lesions and of DWI/PI for identifying salvageable tissue, but that was not possible from the given data. Although it is likely that DWI is more sensitive to acute ischemic stroke than conventional MR or CT, sample sizes were so small, or insufficient details of clinical features, inclusion and exclusion criteria, and unsuccessful examinations were given to enable an accurate estimation of efficacy to be made. As the results of this systematic review show, publications in this field so far tend not to include important methodological details and so may be leading stroke researchers into jumping to conclusions not supported by the data. In many studies, the advanced imaging was not read blinded to the more routine imaging, and there were no details on the order in which imaging was performed. In the studies comparing DWI with conventional MR, if DWI was always performed after conventional imaging (as with studies to date that have compared conventional MR with CT[91]), it is likely DWI would always show more lesions. There was little information on patients unable to complete DWI or PI, and most studies lacked clinical details of patient selection and case mix, with the latter information being very important for several reasons.

First, some conditions that mimic stroke clinically can also manifest abnormalities on DWI.[25,92,93] Few studies mentioned whether any of their prospectively identified patients later turned out not to have had a stroke—though it would be unusual, in a prospective sample even as small as 40, not to find the occasional patient thought initially to have had a stroke who turned out to have a nonvascular cause of the symptoms.[94] Conversely, the study by Ay et al[27] and other case reports[95,96] have highlighted the potential for DWI to be negative in patients with ischemic stroke. Although PI may be of some use in these patients, clarification about this issue is sorely needed.

Second, because stroke is a heterogeneous condition and the case mix of patients is likely to differ between hospitals (even within a small geographical area), this will have led to differences between studies in the type of stroke patients included. However, unless sufficient details of the patients' clinical characteristics at baseline (eg, age, gender, some measure of neurological deficit, prestroke morbidity) and clinical status at a recognized, valid outcome point (eg, 3 months) by a validated outcome score are given, it is impossible to gauge the generalizability of the individual study results and hence the relevance to the stroke population in general. One month after stroke is far too early to determine clinical outcome and still too early for radiological outcome. There may still be either swelling (overestimating final infarct size) or fogging (grossly underestimating final infarct size). In fact, use of *any* radiological outcome is difficult if a volume measure or image coregistration are used, because (in addition to swelling and fogging) loss of volume in the affected area and ex vacuo effects in surrounding tissues from 4 to 6 weeks onward[89] will lead to underestimation of final infarct volume.

Third, the clinical severity of the stroke is a profound determinant of clinical outcome. It correlates strongly with the site and extent of the lesion on CT and structural MR and therefore must be taken into consideration when any new imaging techniques are described. Most studies failed to do this adequately: the NIHSS (the most frequently used neurological score) captures part, but by no means all, of the severity of the patient's stroke; ie, it predicts a proportion but by no means all of the patient's outcome. Stroke severity must be fully adjusted before any additional information contributed by an imaging technique to the identification of particular patients, or the determination of outcome, can be identified.[97] Stroke severity also influences the time to admission to hospital (patients with severe strokes are admitted sooner after stroke than those with milder strokes[98]) and hence will influence the time to imaging. This, in turn, will probably influence the ADC values found in individual patients. The influence of stroke severity cannot be overemphasized: failure to take account of it may have contributed to perceived differences between studies that compared ADC changes over time in which "snapshots" of different patients at different times were used instead of the same patients scanned serially at different times. A similar effect most probably affects the findings in studies of DWI with PI, in which the proportion of patients with diffusion/perfusion mismatch and its size will depend on the severity of stroke and the time delay to imaging.

Although many studies gave ample details of the imaging sequences used, there are problems with the precise DWI or PI parameters to be measured, moreso with PI. Most MR PI techniques measure relative and not absolute perfusion changes, and positron emission tomography studies have demonstrated drawbacks with this approach.[99] Relative perfusion values may not precisely demonstrate which tissue is at greatest risk of infarction, added to which is the unresolved debate about the best parameter of the PI curve to use in the analysis. Attempting to ascribe a physiological mechanism to PI findings on the basis of our current knowledge is to risk mistaking association for causation. Very detailed analysis of small data sets (eg, 30 patients) may be used to generate hypotheses to test in new studies. However, conclusions from such analyses are data dependent in themselves, and placing too much reliance on the results might be misleading,[100] particularly in the absence of any spontaneous or pharmacologically induced tissue recovery to identify which tissue actually is salvageable. An example of this type of error approximately 10 years ago was the overemphasis of the association between hemorrhagic transformation and cardioembolic stroke. Then, it was incorrectly assumed that cardioembolic stroke *caused* hemorrhagic transformation, because of an observed *association,* when in fact the size of the infarct rather than the mechanism per se was responsible.[101,102]

In all cases, particularly in studies of DWI with PI so far, the sample size has been small. Our totals may overestimate the true number imaged, because some patients were included in several different publications. Small sample size makes the studies vulnerable to the play of chance in the mix of patients included and the study results. Examples of how profound an effect the play of chance can have can be found in the systematic review of early trials of thrombolysis for acute myocardial infarction[103] (in which studies with sample sizes up to several hundred had diametrically opposite results) and in an exercise to demonstrate the effect of chance on small sample sizes (DICE [Don't Ignore Chance Effects] therapy).[104] Investigators should be encouraged to combine their existing individual patient data from different individual studies and participate in new multicenter studies whenever possible, thereby achieving much larger sample sizes and overcoming some of the case-mix problems outlined above. The numbers of patients required to obtain more robust data on the efficacy of DWI and/or PI in individual studies are not large, however. Only 84 patients would be required to show (with 90% power) that DWI demonstrated lesions in 90%, as opposed to CT showing lesions in 60% of patients.

Finally, acutely ill patients are poor MR subjects: they are restless, they may be confused and unable to lie still for prolonged scan times, and observing their clinical state is difficult. Lying supine when the ability to protect the airway is impaired increases the risk of aspiration (roughly 50% of all stroke patients have acutely impaired swallowing reflex). DWI and PI have to genuinely provide information over and above that which is readily available on a plain CT, and which alters clinical management, and this information has to outweigh any loss of treatment efficacy resulting from added time delay to start of treatment, if their incorporation into patient management is to be justified. Such a balance has not yet been studied.

So, where do we go from here? Larger studies of DWI with PI are needed, with clear patient clinical details (inclusions, exclusions, and failures), blinding of analyses, valid clinical outcome measures, and comparison with a routine imaging such as CT so that an assessment of added clinical value can be made. Patient status during imaging should be assessed to identify adverse events, such as hypoxia, which could then be treated or avoided. DWI/PI should be evaluated in *randomized* trials of new or existing acute stroke treatments because that will continue to increase the knowledge pool on the practical application of complex imaging, and only then will we actually find out which tissue is still viable and recoverable and which is not. Then and only then will we know, when faced with an individual acute stroke patient, at a certain time after the stroke, with particular clinical features and appearances on DWI/PI, what the best clinical management will be.

Acknowledgments

Dr Keir received funding from the National Coordinating Centre for Health Technology Assessment, a branch of the National Health Service Research and Development body. The statements, opinions, and results in this article are those of the authors and do not reflect the policy or position of the NCCHTA.

References

1. Prichard JW, Grossman RI. New reasons for early use of MRI in stroke. *Neurology.* 1999;52:1733–1736.
2. Provenzale JM, Sorensen AG. Diffusion-weighted MR imaging in acute stroke: theoretic considerations and clinical applications. *AJNR Am J Neuroradiol.* 1999;173:1459–1467.
3. Yuh WTC. The need for objective assessment of the new imaging techniques and understanding the expanding roles of stroke imaging. *AJNR Am J Neuroradiol.* 1999;20:1779–1784.
4. Powers WJ, Zivin J. Magnetic resonance imaging in acute stroke: not ready for prime time. *Neurology.* 1998;50:842–843.
5. Le Bihan D, Breton D, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurological disorders. *Radiology.* 1986;161: 401–407.
6. Edelman RR, Mattle HP, Atkinson DJ, Hill T, Finn JP, Mayman C. Cerebral blood flow: assessment with dynamic contrast-enhanced T2-weighted MR imaging at 1.5 T. *Radiology.* 1990;176:211–220.
7. Siewert B, Schlaug G, Edelman RR, Warach S. Comparison of EPISTAR and T2*-weighted gadolinium-enhanced perfusion imaging in patients with acute cerebral ischemia. *Neurology.* 1997;48:673–9.
8. Cochrane Stroke Group Search Strategy for Specialised Register. *The Cochrane Library*, issue 1, 2000. Oxford, UK: Update Software.
9. White PM, Wardlaw JM, Easton VE. Can non-invasive imaging tests accurately detect intracranial aneurysms? A systematic review. *Radiology.* In press.
10. Barber PA, Darby DG, Desmond PM, Gerraty RP, Yang Q, Li T, Jolley D, Donnan GA, Tress BM, Davis SM. Identification of major ischemic change: diffusion-weighted imaging versus computed tomography. *Stroke.* 1999;30:2059–2065.
11. Muller M, Reiche W, Langenscheidt P, Hassfeld J, Hagen T. Ischaemia after carotid endarterectomy: comparison between transcranial doppler sonography and diffusion-weighted MR imaging. *AJNR Am J Neuroradiol.* 2000;21:47–54.
12. Lovblad KO, Baird AE, Schlaug G, Benfield A, Siewert B, Voetsch B, Connor A, Burzynski C, Edelman RR, Warach S. Ischemic lesion volumes in acute stroke by diffusion-weighted magnetic resonance imaging correlate with clinical outcome. *Ann Neurol.* 1997;42:164–170.
13. Schonewille WJ, Tuhrim S, Singer MB, Atlas SW. Diffusion-weighted MRI in acute lacunar syndromes: a clinical- radiological correlation study. *Stroke.* 1999;30:2066–2069.
14. Chong J, Aragao F, Singer MB, Schonewille WJ, Silvers A, Tuhrim S. Diffusion-weighted MR of acute cerebral infarction: comparison of data processing methods. *AJNR Am J Neuroradiol.* 1998;19:1733–1739.
15. Warach S, Chien D, Li W, Ronthal M, Edelman RR. Fast magnetic resonance diffusion-weighted imaging of acute human stroke. *Neurology.* 1992;42:1717–1723.
16. Geijer B, Brockstedt S, Lindgren A, Stahlberg F, Norrving B, Holtas S. Radiological diagnosis of acute stroke: comparison of conventional MR imaging, echo-planar diffusion-weighted imaging, and spin-echo diffusion-weighted imaging. *Acta Radiol.* 1999;40:255–262.
17. van Everdingen KJ, van der Grond J, Kappelle LJ, Ramos LM, Mali WP. Diffusion-weighted magnetic resonance imaging in acute stroke. *Stroke.* 1998;29:1783–1790.
18. Singer MB, Chong J, Lu D, Schonewille WJ, Tuhrim S, Atlas SW. Diffusion-weighted MRI in acute subcortical infarction. *Stroke.* 1998; 29:133–136.
19. Marks MP, de Crespigny A, Lentz D, Enzmann DR, Albers GW, Moseley ME. Acute and chronic stroke: navigated spin-echo diffusion-weighted MR imaging. *Radiology.* 1996;199:403–408.
20. Lovblad KO, Laubach HJ, Baird AE, Curtin F, Schlaug G, Edelman RR, Warach S. Clinical experience with diffusion-weighted MR in patients with acute stroke. *AJNR Am J Neuroradiol.* 1998;19:1061–1066.
21. Yang Q, Tress BM, Barber PA, Desmond PM, Darby DG, Gerraty RP, Li T, Davis SM. Serial study of apparent diffusion coefficient and anisotropy in patients with acute stroke. *Stroke.* 1999;30:2382–2390.
22. Lovblad KO, Jakob PM, Chen Q, Baird AE, Schlaug G, Warach S, Edelman RR. Turbo spin-echo diffusion-weighted MR of ischemic stroke. *AJNR Am J Neuroradiol.* 1998;19:201–208.
23. de Crespigny AJ, Marks MP, Enzmann DR, Moseley ME. Navigated diffusion imaging of normal and ischemic human brain. *Magn Reson Med.* 1995;33:720–728.
24. Maier SE, Gudbjartsson H, Patz S, Hsu L, Lovblad KO, Edelman RR, Warach S, Jolesz FA. Line scan diffusion imaging: characterization in

healthy subjects and stroke patients. *AJR Am J Roentgenol.* 1998;171: 85–93.
25. Bartylla K, Hagen T, Globel H, Jost V, Schneider G. Diffusion-weighted magnetic resonance imaging for demonstration of cerebral infarcts. *Radiologe.* 1997;37:859–864.
26. Lovblad KO, Remonda L, Heid O, Schneider J, Gonner F, Schroth G. Clinical single-shot diffusion-weighted MRI of the human brain on a short-bore medium-filed imager. *Neuroradiology.* 1999;41:889–894.
27. Ay H, Buonanno FS, Rordorf G, Schaefer PW, Schwamm LH, Wu O, Gonzalez RG, Yamada K, Sorensen GA, Koroshetz WJ. Normal diffusion-weighted MRI during stroke-like deficits. *Neurology.* 1999; 52:1784–1792.
28. Nagesh V, Welch KMA, Windham JP, Levine SR, Hearshen D, Peck D, Robbins K, D'Olhaberriague L, Soltanian-Zadeh H, Boska MD. Time course of ADC_w changes in ischemic stroke: beyond the human eye! *Stroke.* 1998;29:1778–1782.
29. Welch KMA, Windham RA, Knight RA, Nagesh V, Hugg JW, Jacobs M. A model to predict the histopathology of human stroke using diffusion- and T2-weighted magnetic resonance imaging. *Stroke.* 1995; 26:1983–1989.
30. Chien D, Kwong KK, Gress DR, Buonanno FS, Buxton RB, Rosen BR. MR diffusion imaging of cerebral infarction in humans. *AJNR Am J Neuroradiol.* 1992;13:1097–1102.
31. Sorensen AG, Wu O, Copen WA, Davis TL, Koroshetz WJ, Reese T, Rosen BR, Wedeen VJ, Weisskoff RM. Human acute cerebral ischaemia: detection of changes in water diffusion anisotropy by using MR imaging. *Radiology.* 1999;212:785–792.
32. Ricci PE, Burdette JH, Elster AD, Reboussin DM. A comparison of fast spin-echo, fluid-attenuated inversion-recovery, and diffusion-weighted MR imaging in the first 10 days after cerebral infarction. *AJRN Am J Neuroradiol.* 1999;20:1535–1542.
33. Li T-Q, Takahashi AM, Hindmarsh T, Moseley ME. ADC mapping by means of a single-shot spiral MRI technique with application in acute cerebral ischemia. *Magn Reson Med.* 1999;41:143–147.
34. Burdette JH, Elster AD, Ricci PE. Acute cerebral infarction: quantification of spin-density and T2 shine-through phenomena on diffusion-weighted MR images. *Radiology.* 1999;212:333–339.
35. Bammer R, Stollberger R, Augustin M, Simbrunner J, Offenbacher H, Kooijman H, Ropele S, Kapeller P, Wach P, Ebner F, Fazekas F. Diffusion-weighted imaging with navigated interleaved echo-planar imaging and a conventional gradient system. *Radiology.* 1999;211: 799–806.
36. Ulug A, Beauchamp N, Bryan RN, van Zijl PCM. Absolute quantitation of diffusion constants in human stroke. *Stroke.* 1997;28:483–490.
37. Provenzale JM, Engelter ST, Petrella JR, Smith JS, MacFall JR. Use of MR exponential diffusion-weighted images to eradicate T2 "shine-through" effect. *AJR Am J Roentgenol.* 1999;172:537–539.
38. Burdette JH, Ricci PE, Petitti N, Elster AD. Cerebral infarction: time course of signal intensity changes on diffusion-weighted MR images. *AJR Am J Roentgenol.* 1998;171:791–795.
39. Schlaug G, Siewert B, Benfield A, Edelman RR, Warach S. Time course of the apparent diffusion coefficient (ADC) abnormality in human stroke. *Neurology.* 1997;49:113–119.
40. Warach S, Gaa J, Siewert B, Wielopolski P, Edelman RR. Acute human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging. *Ann Neurol.* 1995;37:231–241.
41. O'Uchi T, Kuru Y, Honda S, Hayashi T, Yasuda R. Application of diffusion-weighted EPI to cerebrovascular disease. *Riv Neuroradiol.* 1998;11:241–242.
42. Read SJ, Jackson GD, Abbott DF, Syngeniotis A, Mitchell LA, Fitt GR, Donnan GA. Experience with diffusion-weighted imaging in an acute stroke unit. *Cerebrovasc Dis.* 1998;8:135–143.
43. Gonzalez RG, Schaefer PW, Buonanno FS, Schwamm LH, Budzik RF, Rordorf G, Wang B, Sorensen AG, Koroshetz WJ. Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset. *Radiology.* 1999;210:155–162.
44. Lutsep HL, Albers GW, DeCrespigny A, Kamat GN, Marks MP, Moseley ME. Clinical utility of diffusion-weighted magnetic resonance imaging in the assessment of ischemic stroke. *Ann Neurol.* 1997;41: 574–580.
45. Noguchi K, Nagayoshi T, Watanabe N, Kanazawa T, Toyoshima S, Morijiri M, Shojaku H, Shimizu M, Seto H. Diffusion-weighted echo-planar MRI of lacunar infarcts. *Neuroradiology.* 1998;40:448–451.
46. Lovblad KO, Weber J, Heid O, Mattle HP, Schroth G. Clinical and radiological patterns of human stroke as defined by echo-planar diffusion-weighted MR imaging. *Riv Neuroradiol.* 1998;11:227–230.
47. Yamada N, Imakita S, Sakuma T. Value of diffusion-weighted imaging and apparent diffusion coefficient in recent cerebral infarctions: a correlative study with contrast-enhanced T1-weighted imaging. *AJNR Am J Neuroradiol.* 1999;20:193–198.
48. Fitzek C, Tintera J, Muller-Forell W, Urban P, Thomke F, Fitzek S, Hopf HC, Stoeter P. Differentiation of recent and old cerebral infarcts by diffusion- weighted MRI. *Neuroradiology.* 1998;40:778–782.
49. Altieri M, Metz RJ, Muller C, Maeder P, Meuli R, Bogousslavsky J. Multiple brain infarcts: clinical and neuroimaging patterns using diffusion-weighted magnetic resonance. *Eur Neurol.* 1999;42:76–82.
50. Kidwell CS, Alger JR, Di Salle F, Starkman S, Villablanca P, Bentson J, Saver JL. Diffusion MRI in patients with transient ischemic attacks. *Stroke.* 1999;30:1174–1180.
51. Koudstaal PJ, van Gijn J, Frenken CW, Hijdra A, Lodder J, Vermeulen M, Bulens C, Franke CL, for the Dutch TIA Study Group. TIA, RIND, minor stroke: a continuum, or different subgroups? *J Neurol Neurosurg Psychiatry.* 1992;55:95–97.
52. Ebisu T, Tanaka C, Umeda M, Kitamura M, Fukunaga M, Aoki I, Hiroshi S, Higuchi T, Naruse S, Horikawa Y, Ueda S. Hemorrhagic and nonhemorrhagic stroke: diagnosis with diffusion-weighted and T2-weighted echo-planar MR imaging. *Radiology.* 1997;203:823–828.
53. Okada S, Cho K, Hosaka S, Ito K, Tajima N, Kobayashi S, Kumazaki T, Takahashi Y. Diffusion weighted EPI in early cerebral infarction and intracerebral hemorrhage. *Jpn J Clin Radiol.* 1997;42:1519–1525.
54. Rother J, Guckel F, Neff W, Schwartz A, Hennerici M. Assessment of regional cerebral blood volume in acute human stroke by use of single-slice dynamic susceptibility contrast-enhanced magnetic resonance imaging. *Stroke.* 1996;27:1088–1093.
55. Warach S, Li W, Ronthal M, Edelman RR. Acute cerebral ischemia: evaluation with dynamic contrast-enhanced MR imaging and MR angiography. *Radiology.* 1992;182:41–47.
56. Wu RH, Bruening R, Berchtenbreiter C, Weber J Steiger HJ, Peller M, Penzkofer H, Reiser M. MRI assessment of cerebral blood volume in patients with brain infarcts. *Neuroradiology.* 1998;40:496–502.
57. Sorensen AG, Wray SH, Weisskoff RM, Boxerman JL, Davis TL, Caramia F, Kwong KK, Stern CE, Baker R, Breiter H, Gazit IE, Belliveau JW, Brady TJ, Rosen BR. Functional MR of brain activity and perfusion in patients with chronic cortical stroke. *AJNR Am J Neuroradiol.* 1995;16:1753–1762.
58. Guckel F, Brix G, Rempp K, Deimling M, Rother J, Georgi M. Assessment of cerebral blood volume with dynamic susceptibility contrast enhanced gradient-echo imaging. *J Comput Assist Tomogr.* 1994;18:344–351.
59. Berthezene Y, Nighoghossian N, Damien J, Derex L, Trouillas P, Froment JC. Effects of thalamic hemorrhage on cortical hemodynamic parameters assessed by perfusion MR imaging: preliminary report. *J Neurol Sci.* 1998;157:67–72.
60. Reith W, Heiland S, Erb G, Benner T, Forsting M, Sartor K. Dynamic contrast-enhanced T2*-weighted MRI in patients with cerebrovascular disease. *Neuroradiology.* 1997;39:250–257.
61. Soher BJ, Gillard JH, Bryan RN, Oppenheimer SM, Barker PB. Magnetic resonance perfusion imaging in acute middle cerebral artery stroke: comparison of blood volume and bolus peak arrival time. *J Stroke Cerebrovasc Dis.* 1998;7:17–33.
62. Nighoghossian N, Berthezene Y, Adeleine P, Wiart M, Damien J, Derex L, Itti R, Froment JC, Trouillas P. Effects of subcortical cerebrovascular lesions on cortical hemodynamic parameters assessed by perfusion magnetic resonance imaging. *Cerebrovasc Dis.* 1999;9:136–141.
63. Hacklander T, Hofer M, Reichenbach JR, Rascher K, Furst G, Modder U. Cerebral blood volume maps with dynamic contrast-enhanced T1-weighted FLASH imaging: normal values and preliminary clinical results. *J Comput Assist Tomogr.* 1996;20:532–539.
64. Schreiber WG, Guckel F, Stritzke P, Schmiedek P, Schwartz A, Brix G. Cerebral blood flow and cerebrovascular reserve capacity: estimation by dynamic magnetic resonance imaging. *J Cereb Blood Flow Metab.* 1998;18:1143–1156.
65. Yamada H, Koshimoto Y, Sadato N, Kawashima Y, Tanaka M, Tsuchida C, Maeda M, Yonekura Y, Ishii Y. Crossed cerebellar diaschisis: assessment with dynamic susceptibility contrast MR imaging. *Radiology.* 1999;210:558–562.
66. Tsuchida C, Yamada H, Maeda M, Sadato N, Matsuda T, Kawamura Y, Hayashi N, Yamamoto K, Yonekura Y, Ishii Y. Evaluation of peri-

infarcted hypoperfusion with T2*-weighted dynamic MRI. *J Magn Reson Imaging.* 1997;7:518–522.
67. Hatazawa J, Shimosegawa E, Toyoshima H, Ardekani BA, Suzuki A, Okudera T, Miura Y. Cerebral blood volume in acute brain infarction: a combined study with dynamic susceptibility contrast MRI and ^{99m}Tc-HMPAO-SPECT. *Stroke.* 1999;30:800–806.
68. Kim J, Shin T, Park J, Chung S, Choi N, Lim B. Various patterns of perfusion-weighted MR imaging and MR angiographic findings in hyperacute ischaemic stroke. *AJNR Am J Neuroradiol.* 1999;20: 613–620.
69. Hagen T, Bartylla K, Piepgras U. Correlation of regional cerebral blood flow measured by stable xenon CT and perfusion MRI. *J Comput Assist Tomogr.* 1999;23:257–264.
70. Wang AM, Shetty AN, Woo H, Rao SK, Manzione JV, Moore JR. Diffusion weighted MR imaging in evaluation of CNS disease. *Riv Neuroradiol.* 1998;11:109–112.
71. Darby DG, Barber PA, Gerraty RP, Desmond PM, Yang Q, Parsons M, Li T, Tress BM, Davis SM. Pathophysiological topography of acute ischemia by combined diffusion-weighted and perfusion MRI. *Stroke.* 1999;30:2043–2052.
72. Flacke S, Keller E, Hartmann A, Murtz P, Textor J, Urbach H, Folkers P, Traber F, Gieseke J, Block W, Scheef L, Leutner C, Pauleit D, Schild HH. Improved diagnosis of early cerebral infarct by the combined use of diffusion and perfusion imaging. *Fortschr Rontgenstr.* 1998;168: 493–501.
73. Schellinger PD, Jansen O, Fiebach JB, Hacke W, Sartor K. A standardized MRI stroke protocol: comparison with CT in hyperacute intracerebral hemorrhage. *Stroke.* 1999;30:765–768.
74. Sunshine JL, Tarr RW, Lanzieri CF, Landis DMD, Selman WR, Lewin JS. Hyperacute stroke: ultrafast MR imaging to triage patients prior to therapy. *Radiology.* 1999;212:325–332.
75. Karonen JO, Vanninen RL, Liu Y, Ostergaard L, Kuikka JT. Combined diffusion and perfusion MRI with correlation to single-photon emission CT in acute ischemic stroke. *Stroke.* 1999;30:1583–1590.
76. Ueda T, Yuh WTC, Maley JE, Quets JP, Hahn PY, Magnotta VA. Outcome of acute lesions evaluated by diffusion and perfusion MR imaging. *AJNR Am J Neuroradiol.* 1999;20:983–989.
77. Sorensen AG, Copen WA, Ostergaard L, Buonanno FS, Gonzalez RG, Rordorf G, Rosen BR, Schwamm LH. Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow, and mean tissue transit time. *Radiology.* 1999;210:519–527.
78. Rordorf G, Koroshetz WJ, Copen WA, Cramer SC, Schaefer PW, Budzik RF. Regional ischemia and ischemic injury in patients with acute middle cerebral artery stroke as defined by early diffusion-weighted and perfusion-weighted imaging. *Stroke.* 1998;29:939–943.
79. Baird AE, Benfield A, Schlaug G, Siewert B, Lovblad KO, Edelman RR. Enlargement of human cerebral ischemic lesion volumes measured by diffusion-weighted magnetic resonance imaging. *Ann Neurol.* 1997; 41:581–589.
80. Sorensen GA, Buonanno FS, Gonzalez RG, Schwamm LH, Lev MH, Huang-Hellinger FR. Hyperacute stroke: evaluation with combined multisection diffusion-weighted and hemodynamically weighted echo-planar MR imaging. *Radiology.* 1996;199:391–401.
81. Warach S, Dashe JF, Edelman RR. Clinical outcome in ischemic stroke predicted by early diffusion-weighted and perfusion magnetic resonance imaging: a preliminary analysis. *J Cereb Blood Flow Metab.* 1996;16: 53–59.
82. Schwamm LH, Koroshetz WJ, Sorensen G, Wang B, Copen WA. Time course of lesion development in patients with acute stroke: serial diffusion- and hemodynamic-weighted magnetic resonance imaging. *Stroke.* 1998;29:2268–2276.
83. Barber PA, Davis SM, Darby DG, Desmond PM, Gerraty RP, Yang Q, Jolley D, Donnan GA, Tress BM. Absent middle cerebral artery flow predicts the presence and evolution of the ischemic penumbra. *Neurology.* 1999;52:1125–1132.
84. Barber PA, Darby DG, Desmond PM, Yang Q, Gerraty RP, Jolley D. Prediction of stroke outcome with echoplanar perfusion- and diffusion-weighted MRI. *Neurology.* 1998;51:418–426.
85. Jansen O, Schellinger PD, Fiebach JB, Hacke W, Sartor K. Early recanalisation in acute ischaemic stroke saves tissue at risk defined by MRI. *Lancet.* 1999;353:2036–2037.
86. Beaulieu C, de Crespigny A, Tong DC, Moseley ME, Albers GW, Marks MP. Longitudinal magnetic resonance imaging study of perfusion and diffusion in stroke: evolution of lesion volume and correlation with clinical outcome. *Ann Neurol.* 1999;46:568–578.
87. Neumann-Haefelin T, Wittsack H-J, Wenserski F, Siebler M, Seitz RJ. Diffusion- and perfusion-weighted MRI: the DWI/PWI mismatch region in acute stroke. *Stroke.* 1999;30:1591–1597.
88. Tong DC, Yenari MA, Albers GW, O'Brien M, Marks MP, Moseley ME. Correlation of perfusion- and diffusion weighted MRI with NIHSS score in acute (<6.5 hour) ischemic stroke. *Neurology.* 1998;50: 864–870.
89. Wardlaw JM. What pathological type of stroke is it? In: Warlow CP, Dennis MS, Hankey GJ, Sandercock PAG, van Gijn J, Wardlaw JM, eds. *Stroke: A Practical Guide to Management.* Oxford, UK: Blackwell Scientific Ltd; 1996:146–189.
90. Pereira AC, Doyle VL, Griffiths JR, Brown MM. Disappearing cerebral infarcts: a longitudinal MRI study of 16 patients. *Cerebrovasc Dis.* 1997;7:30. Abstract.
91. Mohr JP, Biller J, Hilal SK, Yuh WTC, Tatemichi TK, Hedges S. Magnetic resonance versus computed tomographic imaging in acute stroke. *Stroke.* 1995;26:807–812.
92. Lansberg MG, O'Brien MW, Norbash AM, Moseley ME, Morrell M, Albers GW. MRI abnormalities associated with partial status epilepticus. *Neurology.* 1999;52:1021–1027.
93. Lim CC, Sitoh YY, Lee KE, Kurup A, Hui F. Meningoencephalitis caused by a novel paramyxovirus: an advanced MRI case report in an emerging disease. *Singapore Med J.* 1999;40:356–358.
94. Libman RB, Wirkowski E, Alvir J, Rao TH. Conditions that mimic stroke in the emergency department: implications for acute stroke trials. *Arch Neurol.* 1995;52:1119–1122.
95. Lefkowitz D, LaBenz M, Nudo SR, Steg RE, Bertoni JM. Hyperacute ischemic stroke missed by diffusion-weighted imaging. *AJNR Am J Neuroradiol.* 2000;20:1871–1875.
96. Wang PY, Barker PB, Wityk RJ, Ulug AM. Diffusion-negative stroke: a report of two cases. *AJNR Am J Neuroradiol.* 2000;20:1876–1880.
97. Wardlaw JM, Lewis SC, Dennis MS, Counsell C, McDowall M. Is visible infarction on computed tomography associated with an adverse prognosis in acute ischemic stroke? *Stroke.* 1998;29:1315–1319.
98. Uchino K, Cramer SC. Entry criteria and baseline characteristics predict outcome in acute stroke trials. *Stroke.* 2000;31:277. Abstract.
99. Powers WJ, Grubb RL Jr, Raichle ME. Physiological responses to focal cerebral ischemia in humans. *Ann Neurol.* 1984;16:546–552.
100. Marchal G, Benali K, Iglesias S, Viader F, Derlon JM, Baron JC. Voxel-based mapping of irreversible ischaemic damage with PET in acute stroke. *Brain.* 1999;122(pt 12):2387–2400.
101. Lodder J, Krijne-Kubat B, Broekman J. Cerebral hemorrhagic infarction at autopsy: cardiac embolic cause and the relationship to the cause of death. *Stroke.* 1986;17:626–629.
102. Lodder J. CT detected haemorrhagic infarction: relation with size of infarct and the presence of midline shift. *Acta Neurol Scand.* 1984;70: 329–335.
103. Yusuf S, Collins R, Peto R, Furburg C, Stampfer MJ, Goldhaber SZ. Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction and side effects from 33 randomised controlled trials. *Eur J Cardiol.* 1985;6:556–585.
104. Counsell C, Clarke MJ, Slattery J, Sandercock PAG. The miracle of DICE for acute stroke therapy: fact or fictional product of subgroup analysis? *BMJ.* 1994;309:1677–1681.